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1. Ford, R. V., and Moyer, J. H.: Am. Heart J. 46:754 (Nov.) 1953.
2. Crawley, C. J., *et al.*: New York State J. Med. 54:220 (Aug. 1) 1954.

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1. O'Brien, G. F., and Schweitzer, I. L.: M. Clin. North America *37*:155 (Jan.) 1953.
2. Rising, J. D.: Missouri Med. *51*:52, 1954.
3. Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, Philadelphia, Lea & Febiger, 1953, p. 49.

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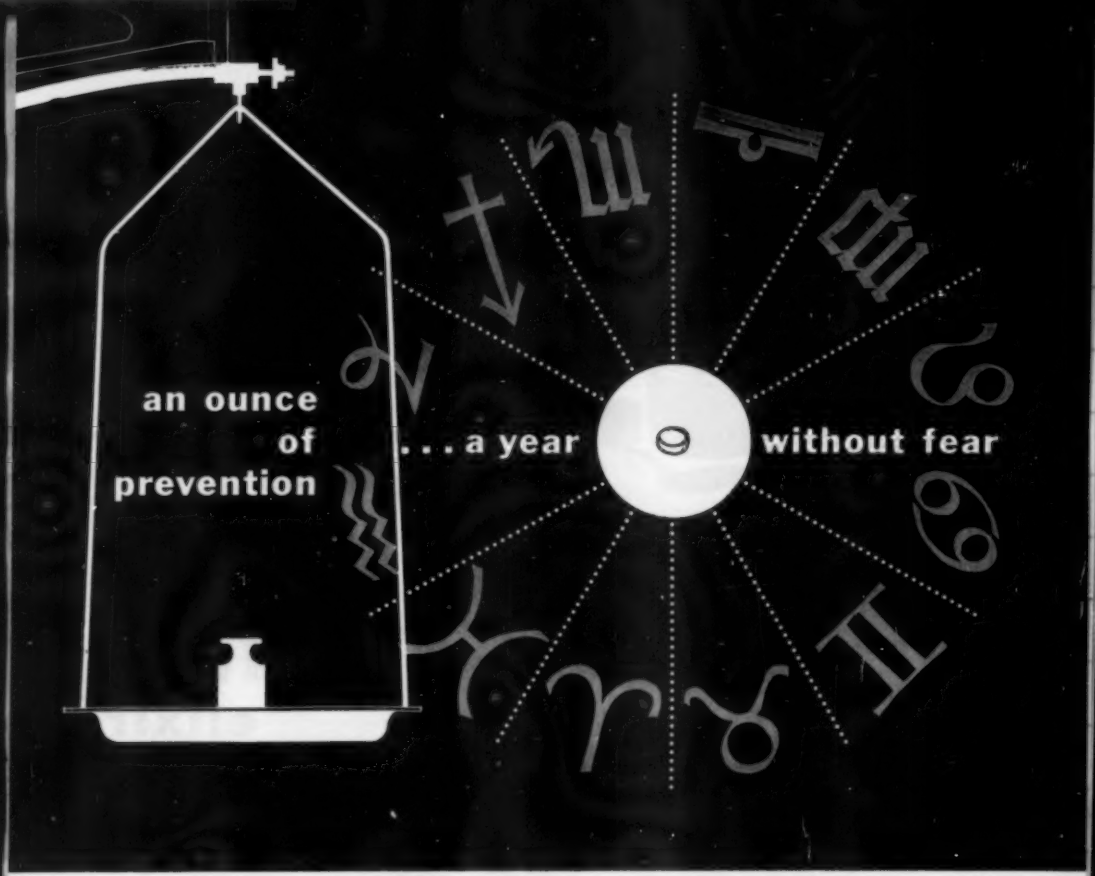

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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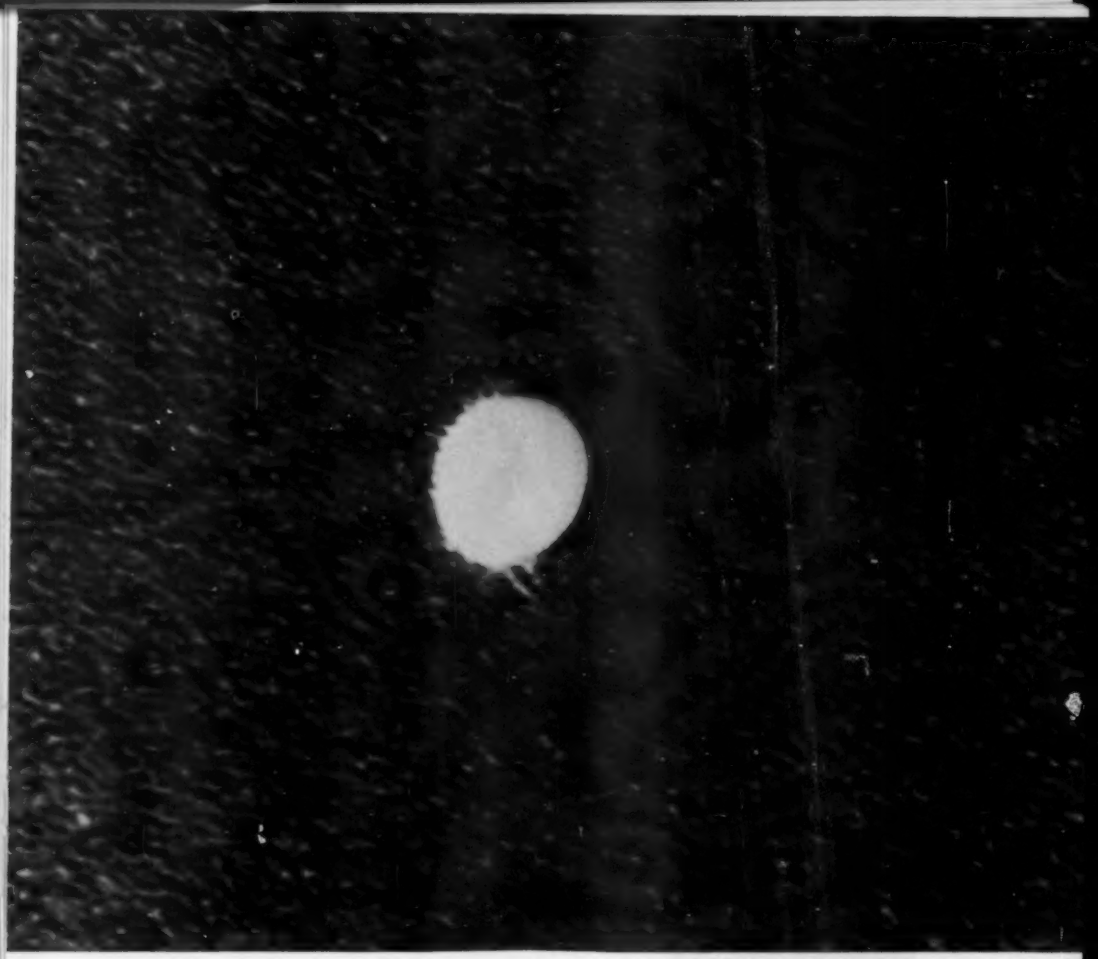

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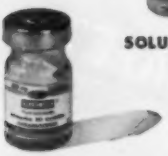

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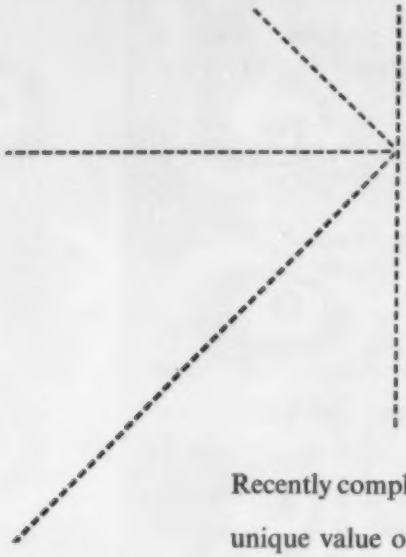

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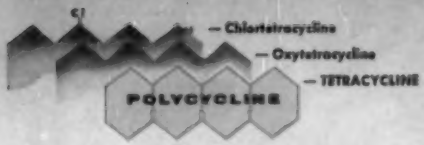

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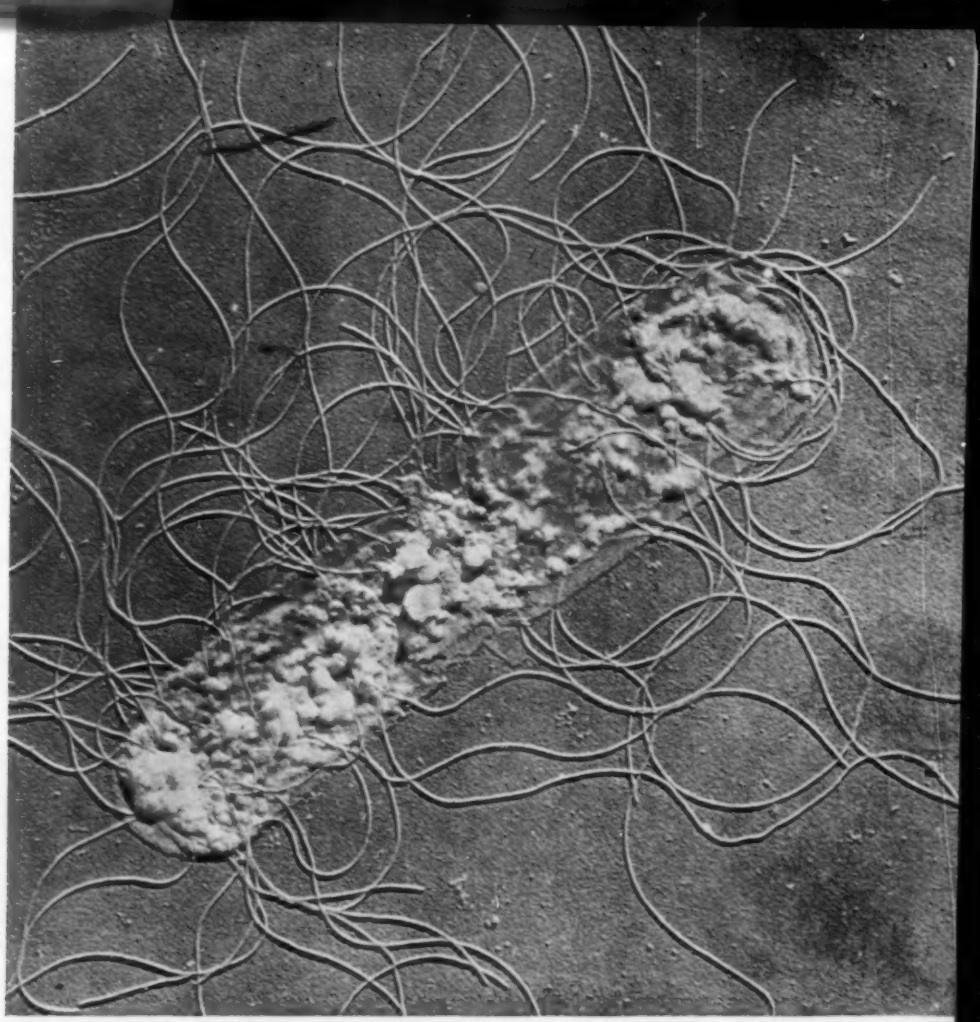

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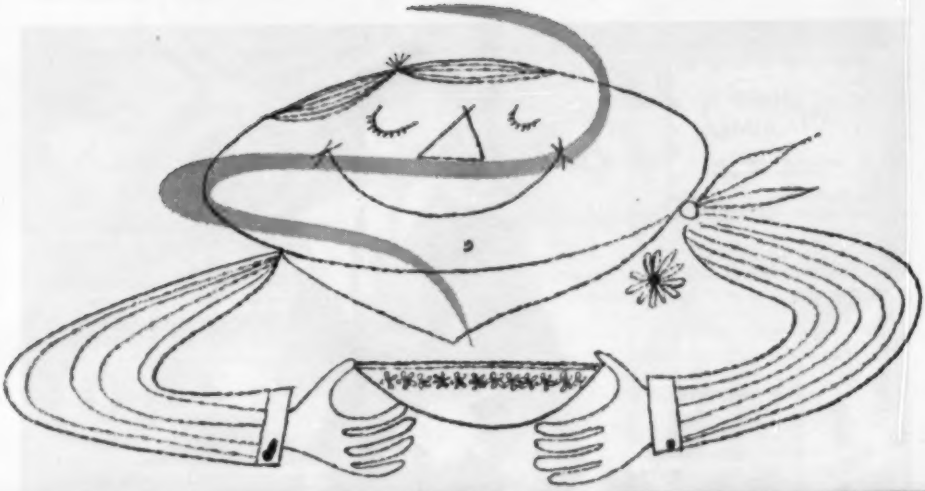

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ANNALS OF
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VOLUME 41 DECEMBER, 1954 NUMBER 6

PITFALLS AND PROGRESS IN CANCER CONTROL *

By C. P. RHOADS, M.D., F.A.C.P., *New York, N. Y.*

CANCER research has become a major enterprise as a result of public determination to carry over to the problems of peace the progress made by the determined and extensive scientific effort of the recent war. Federal and State funds have been appropriated and private philanthropic organizations created to achieve, by the scientific method, cancer control in man. Sufficient time has now elapsed to permit an evaluation of some of the pitfalls encountered and of the progress made.

The first problem was how to organize the effort. Whereas all concerned were satisfied that the cancer control so ardently desired would be accomplished only by scientific investigation, there was no unanimity of opinion as to how this should be arranged, managed and financed. There were two possibilities: one was to conduct the research as a university function coördinate with teaching, and the other to pursue it in the industrial laboratories more rigidly committed to the achievement of specific goals. For a pharmaceutic house to seek a cancer cure, however, may be fiscally difficult, since the outlay required is large and the possibility of achieving its return distinctly slight. No industry could restrict a life-saving drug to sale at a profit only.

It was apparent, therefore, that the major expense of cancer research would have to be met by public funds, derived from either taxation or solicitation of the citizens. Those in charge decided that these funds should not be expended in commercial organizations, and they turned, consequently, to the universities.

The productive use of the university system in a *program* of research to achieve a definite end, such as the control of cancer, presents certain problems, however. The university is by tradition the protector of the

* Presented at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 5, 1954.

freedom of the individual investigator, and the opponent of plan and program except under extreme duress. Furthermore, its function is to teach and, since teaching is arranged by technical subject, the original framework of the academic organization grew by subject rather than by problem. New knowledge in a teaching institution is sought as an end in itself. The research program is therefore organized under subject divisions, such as chemistry or physics, and not by the ends to be achieved through their use, such as antibiotics or atom bombs. With the decision to employ the university system to gain control of cancer, therefore, the effort was inevitably organized by academic subject in the classic divisions, such as anatomy, biology, chemistry and physics. This was done in the expectation that, as new information in these subjects developed, some would pertain to the cancer problem. This pertinence, it was assumed, would be apparent to all, and would be converted promptly to practical application in cancer control. The organization of medical research by technical division is strong and relatively inflexible, however, and individualism is deeply ingrained. Technic may become an end in itself and, even though aided by cancer funds, may not always be employed to make an end to cancer. Hence, the *management* of a *program* to achieve a specific end, such as cancer control, with the necessarily constant shift of emphasis to exploit new observations, has been difficult.

Furthermore, a system of small grants-in-aid made by a central committee to distant individual investigators has been employed, grants distributed to some extent on a geographic basis. This was done on the assumption that no leads to cancer control were at hand, and so one researcher —if reliable—was as good as another. The magic discovery, it was thought, would be a matter of luck anyway, and so the smaller the bets, the more could be placed, and the better the chance of a jack-pot. Actually, of course, the history of medical research is replete with evidence in refutation of this theory.

Substantial progress has been made in overcoming this first pitfall, that of allocating research to control cancer by academic subject rather than mobilizing the subjects to attack cancer. Major grants, sometimes termed "institutional," have been made to universities, without a defined plan of expenditure, to stimulate internal coöperation of cancer effort. It was expected that the chemist, the physicist and the biologist would work together and, since they received support from cancer funds, that they would apply promptly the knowledge thereby achieved to attaining the goal of cancer progress. This support has been most fruitful in the extension of fundamental knowledge.

To overcome the deficiencies of the multiple small grants-in-aid system as the *only* mode of aiding research to solve the specific problem, a number of institutions for cancer research now have been established. This development is so recent that at the moment it is hard to tell how effective it

will be. It is already clear, however, that if these institutions are properly organized and staffed, and if they are permitted continuity of work, with individual initiative, very considerable progress can be made.

The second pitfall encountered was the widely held, and stultifying, belief that nothing could be accomplished in cancer control until some revolutionary new discovery of the most fundamental nature was made. Such clichés as "the riddle of cancer" or "a problem as obscure as the nature of life itself" were, and still are, bandied about.

Many have now come to believe, however, and with good reason, that the hopeless point of view concerning the cancer problem is not entirely in order. Rather, it is now held that there is already more than enough pertinent information, so many obvious and important leads, that the most intense and orderly effort is entirely justified to convert available new knowledge to new applications in the control of cancer in man.

Progress in overcoming the mystery concept of cancer is taking place at an increasingly rapid rate. Most important in this progress is the replacement of the melancholy and defeatist tradition by the constructive conviction that the cancer cell can be attacked as just another invading microorganism. It is now viewed by some as being as characteristically different from the normal body cell as is the pneumococcus or the tubercle bacillus, and so potentially as susceptible to selective chemical destruction.

The most impressive evidence in support of this view is at hand in the modern procedures of growing human neoplastic cells outside of the human body because, by doing so, Koch's postulates can be fulfilled. Compliance with these requirements, laid down by Koch in 1880, has been and still is regarded as conclusive proof that a particular biologic entity is causative of a disease process, and that the destruction of the organism must be achieved if cure is to be attained. These postulates are three:

(1) That the organism be demonstrable regularly in the diseased tissue itself;
(2) That it be susceptible to culture outside of the body;
(3) That it induce the characteristic disease when re-inoculated.

These postulates have now been fulfilled for the cancer cell in neoplastic disease as completely as they were for the tubercle bacillus in tuberculosis 70 years ago.

The fulfillment of the first postulate is obvious enough to anyone who cares to observe a section of tissue involved by cancer cells. The reaction of the normal structures is vigorous as to both stroma formation and infiltration by inflammatory cells.

The second postulate has now been fulfilled completely.

Gey [1] has described the sustained culture of cells derived from an original implant of cancer of the human uterine cervix. On purely morphologic grounds, these were presumed to be neoplastic cells. They now grow so

well as to permit their use in many laboratories as a peculiarly suitable medium for the cultivation of viruses. More recently, Southam [2] in our laboratories, Murray [3] and Pomerat [4] have described the transient cultivation of cells of several types of human neoplasm. Now Moore [5] in our laboratories has carried for long periods of time six different strains of human cancer cells in pure culture.

In all these instances, however, it was extremely difficult to be certain that the cells cultivated were still characteristically human and truly neoplastic, still capable of inducing, upon inoculation in man, disease of the type originally explanted. Two crucial experiments have now been performed, which apparently have settled this question at last.

For many years means have been sought for maintaining human cancer in experimental animals, on a large scale and for prolonged periods, in order to permit reproducible experiments in biology and therapy. Toolan [6] of our institution has recently made a distinguished contribution to this field by devising means for the successful transplantation of human cancer tissue to the irradiated laboratory animal.

More recently, the use of cortisone has been substituted for irradiation and even greater success has been achieved. In the rat or hamster, human cancer tissue will grow regularly and establish definite, though small, deposits of new cells. By the proper choice of animal and by the use of human tumors with a high innate growth potential, so handled as to increase the growth rate of the neoplastic cells at the expense of the limiting human stroma, four different strains of human neoplasms have been established in mass culture. Three of epidermoid cancer and one of fibrosarcoma have been in mass transplantation for over one year. An inoculation of 100 mg. of tissue today will yield upwards of 5 gm. 14 days hence. In this way literally pounds of human cancer are now being harvested each month. Metastasis does occur.

The all-important question still remained, however, of whether cultured cancer cells, so long removed from man, retain their human as well as their neoplastic characteristics and so would fulfill the third postulate of Koch. A second, and now classic, experiment gave the answer. A patient came under study with widely invasive cancer of the uterine cervix, which had metastasized to both groins. Since the situation was therapeutically hopeless, it was her desire that she participate in any studies which might be useful to humanity as a whole. Accordingly, she permitted the repeated surgical removal of specimens of her cancer tissue for culture and for transplantation to suitably prepared laboratory animals. Both procedures were successful, and substantial growth of the transplants occurred. After four months in culture, when the growth potential and viability of the cancer were well established, the cells were back-transplanted into the subcutaneous tissue of the patient. Active growth took place of a morphologically true cancer, identical with that removed at biopsy so long before. This can be

done, not only for epidermoid but also for other neoplasms. These experiments are regarded as adequate proof that the neoplastic cells, so long under artificial cultivation and so many generations removed from the original transplant, have retained both their human and their neoplastic properties. Ample evidence exists that for tissue to grow upon transplantation, it must be identical with that of the recipient.

We present these experiments as fulfillment of the third of Koch's postulates for the neoplastic cell in man. The cells present in and characteristic of the lesion have now been cultivated outside of the human body, both in glass and in animals, and moreover, upon re-inoculation in animals and in man they have reproduced the disease in every detail, including metastasis in animals. We submit that this fulfillment justifies an orderly effort to achieve cancer control by means (chemotherapy) which have already been amply established as effective in controlling disease due to invasion of the body by other forms of parasitic microörganisms. It gives us an experimental approach never before at hand.

The third pitfall impeding cancer research has been the conviction, long held, that a neoplasm must be an autonomous growth, insusceptible to control by those factors which normally limit the reproduction of tissue. This concept has enhanced the general and unfounded pessimism regarding potential cancer control.

Progress toward the demolition of the idea of essential autonomy has been substantial, with the consequent appearance of a more hopeful point of view. Almost 60 years ago Beatson [7] described the retrogression of mammary cancer following ovarian extirpation, adequate evidence that this neoplasm at least is not necessarily wholly autonomous. Although the observation was made over and over again, its implication was unrecognized until its application by Huggins [8] in 1939 to the control of prostatic cancer by feminization, and later by Treves [9] similarly to cancer of the male breast.

New evidence came forward when Adair and Herrmann [10] of our institution proved that the administration of testosterone to patients with advanced mammary cancer would induce objectively demonstrable, transient improvement in something over 20 per cent. Subsequently, British workers proved that in women well past the menopause, estrogenically active compounds also could cause temporary remissions.[11]

More recently Huggins [12] has shown that adrenalectomy is followed by improvement in certain patients with disseminated breast disease. The observation was confirmed and extended by Pearson, Randall and their co-workers [13] in our laboratories. They proved conclusively that adrenalectomy may be effective after resistance to the effects of ovarian or testicular ablation has developed. At the present time this group and, independently, the one in Stockholm [14] are obtaining suggestive evidence that hypophysectomy may exert an additional effect.

Furthermore, in our laboratories, knowledge of cancer dependence has been advanced by the ingenious development and use of a delicate method for measuring precisely the effect of a procedure on the rate of growth of any osteolytic neoplasm.[15] This is based on the change in blood levels and excretion rates of calcium. The procedure shows clearly the powerful effect exerted upon the growth of mammary cancer by even physiologic levels of estrogenic hormones. Even the normal variations in hormone production which mark the phases of the menstrual cycle can be shown to exert a profound influence. In view of these observations, it is impossible to regard cancer of the breast and prostate as necessarily completely autonomous, although it must be understood that in both sites it invariably becomes autonomous eventually.

Rawson and Rall [16] further have made an invaluable contribution to the field of the dependence of tumors by their demonstration that in many instances cancer of the thyroid gland can be induced to take up iodine by those stimuli from the pituitary gland which exert a similar effect upon normal thyroid tissue.

In the field of experimental oncology, similarly convincing evidence of the dependence of induced neoplasms upon their hormonal environment is available.[17] Many transplantable tumors of the pituitary, of the ovary, of the interstitial cells of the testis and of the adrenal require for growth the stimuli normally necessary for maintaining the integrity of those tissues. Here again, however, dependence is only relative and autonomy regularly appears in time.

It is difficult at this moment to see how further to employ therapeutically the principle of continued dependence of certain types of neoplasms beyond the level of effectiveness presently achieved. Inhibition, rather than complete destruction, is the most that can be obtained now, and resistance invariably occurs.

The fourth pitfall encountered by cancer research is the fixed idea that since neoplastic cells are derived originally as abnormal offspring of normal ones, exactly as sports (mutants) occur in all living forms, their selective destruction by chemical means analogous to bacterial chemotherapy must be impossible. The same defeatist point of view has been expressed since the days of Pasteur concerning the possibility of chemical control of bacterial or parasitic disease. Invariably it has proved to be wrong, and we expect that it will be similarly proved wrong in the case of cancer. Furthermore, recent evidence supports this expectation.

Innumerable studies in our laboratories and in others [18] now prove that a single genetic change in bacteria, the most minor mutation possible, and one in principle analogous to the change from normal to neoplastic mammalian cells, yields new strains with wholly different susceptibilities to specific biochemical injury (chemotherapy).

Similar observations for mammalian cells have now been made under

this program by Biesele.[19] Normal and cancer cells of experimental animals have been grown side by side in roller tube cultures at the same rates as judged by mitotic counts. Certain chemicals, proved to be normally employed as essential nutrients by these cells, were then slightly modified to convert them to potential antimetabolites (poisons), in the hope that they would act as injuriously to the cancer cells as sulfanilamide does to some bacteria. Certain of these chemicals did prove selectively to injure the neoplastic cells, in concentrations which were almost without effect on the normal analogues. Finally, the recent studies of Clarke, Philips, Sternberg, Stock, Elion and Hitchings [20] prove that similarly selective anticancer effects can be achieved in vivo. Certain transplantable neoplasms in experimental animals now can be wholly destroyed (cured) without exerting the slightest detectable adverse effect upon the hosts.

Finally, unequivocal proof is at hand that a similarly selective, though temporary, therapeutic effect can be worked against at least one human neoplasm—acute leukemia in children. In this disease the criteria for response are absolute and unmistakable. We know from the results of Tivey [21] that, previous to the availability of effective therapeutic measures, less than 5 per cent of the children with acute leukemia survived for 12 months. Subsequent to the availability of the compounds with anti-folic activity, prepared by the Lederle Laboratories and first employed by Farber,[22] over 20 per cent of the patients survived a year. Some increase in this figure was obtained following the discovery in our laboratories that cortisone-ACTH [23] is also effective. In January, 1953, a new compound, 6-Mercaptopurine (6-MP) became available from the coöperative studies of the Wellcome Research Laboratories with our institution under a program of experimental cancer chemotherapy organized and directed by C. Chester Stock. Over 50 per cent of the patients treated since, employing all three measures, are still surviving past the one-year period, and to date they have shown no demonstrable tendency to relapse, although they may do so at any time.[24]

The compound 6-Mercaptopurine is the first to come into existence upon a rational basis, that of the ability of compounds of similar types selectively to injure specific types of neoplastic cells. Alone, or in combination, it will restrain the growth rate of—and in some cases cure—a number of experimental tumors in animals. It effects remissions in at least one neoplasm in humans. It is impossible, therefore, to regard the cancer cell any longer as, in principle, insusceptible to specific chemotherapeutic attack, although we do not have effective agents today for man.

It has been argued that the temporary remissions which are now being achieved in acute leukemia throughout the world are not worth while, and that the effort to induce them is morally reprehensible. With this point of view few parents or afflicted individuals agree. In the very extensive studies which have been made in our institution, we have never yet en-

countered a patient, or parents, who voiced anything but the most insistent demand that everything possible be done to prolong life or to lessen distress, even if only for days. Not only are these remissions desired, and welcomed when achieved, but the very fact of their achievement, limited and transient though it be, gives hope and encouragement to the sincere worker toward cancer control. Finally, it gives the experimental cancer chemotherapist an invaluable tool for the objective evaluation of candidate chemotherapeutic agents and reliable evidence that their future development is possible. Despite every type of social and moral upheaval, the scientific clock has never yet turned back. It is unlikely to do so in this instance.

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BALLISTOCARDIOGRAPHY: PAST, PRESENT, FUTURE *

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BALLISTOCARDIOGRAPHY has clearly reached a crossroads in its life. It is appropriate, therefore, to present a stock-taking appraisal of this relatively new laboratory technic. Many of you have already been called upon by patients and professional colleagues to pass judgment on the use of the ballistocardiograph in clinical practice, and the need for some knowledge about it is sure to increase. Some of the medical writing to date and the claims by some instrument salesmen are persuasively convincing of its value. The literature is rapidly expanding, and many of the opinions it contains are conflicting or confusing. "Ballistocardiogram" has become part of the informed patient's medical jargon, and it is not uncommon for him to ask you why you have failed to record a ballistocardiogram as part of your study. In fact, one of the popular lay magazines recently published an article in which it was suggested that a physical check-up could not be complete without a ballistocardiogram.

Ballistocardiography is admittedly a controversial subject. The technic clearly provides information about the circulation not obtainable by other readily available clinical methods. This has led to precipitous clinical use by some physicians, with the inescapable result that diagnostic and prognostic claims have been made without clear justification. Opposed to this attitude are those who approach its clinical use with great caution and employ it as a research tool to try to learn more about the method and its possible application to cardiac disease. The group for which I speak is emphatically in this latter category.

One can only speculate as to how many centuries ago some astute physician stood by the bed of a patient with aortic insufficiency or hyperthyroidism and noticed that the bed shook synchronously with the heartbeat. But it is known that the English observer, Parry,[1] recorded this phenomenon in hyperthyroidism in 1786. The first publication of ballistic tracings was in 1877 by Gordon,[2] whose interest was aroused by the observation that a man standing on a spring weighing scale moved the indicator needle synchronously with the heart beat. Gordon suspended a light platform by

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This presentation is based on the work of a group consisting of B. M. Baker, Jr., W. R. Scarborough, S. A. Talbot, F. W. Davis, Jr., R. E. Mason, D. C. Deuchar, S. A. Lore and M. L. Singewald, supported in part by a grant (H-327) from the National Heart Institute, National Institutes of Health, Public Health Service, and in part by a grant from the Life Insurance Medical Research Foundation. Dr. Scarborough and Dr. Deuchar are Howard Hughes Foundation Fellows.

ropes from the ceiling, placed a man on it, and recorded the movements of the platform. Subsequently, a number of workers, using a variety of instruments, recorded body movements produced by the heart and circulation. Among these early workers were Henderson,[3] Satterthwaite,[4] Abramson[5] and others. However, no real advances in the field were made until Starr and his associates,[6] who coined the word "ballistocardiogram," reported their investigations in 1939.

For a time, the field was explored largely by Starr in a careful investigative way. Nickerson[7] and Dock[8] have contributed greatly to the accumulated knowledge in the field. The introduction of the direct body type of instrument, a significant development in the discipline, started a small avalanche of papers on every aspect of the subject.

At the present time, three types of the ballistocardiograph are in common use: (1) the Starr High Frequency Undamped Bed; (2) the Low Frequency Critically Damped Bed of Nickerson, and (3) the Direct Body Pick-up, proposed and popularized by Dock. (Records may be recorded as displacement of the body or as velocity or acceleration.) The use of these three types of ballistocardiographs in the clinic has led to the accumulation of extensive empirical data on various disease states. The results of analysis and study of these data from many clinics are somewhat discouraging. Thus far, the ballistocardiogram has made little contribution to knowledge of valvular heart disease or of congenital heart disease, with the exception of coarctation of the aorta, in which a reasonably definite pattern is frequently found.

Many research groups have been intensively investigating the ballistocardiograph as a means of bridging a vital gap in the management of patients with coronary artery disease. Every experienced clinician knows all too well that he is virtually powerless to predict the outcome of this disease. He never knows when it may appear in those he examines and finds to be apparently normal. Ballistocardiography has aroused keen interest because it provides a new and different kind of information about the functional state of the circulatory system, related to the pumping action of the heart. This interest was considerably sharpened by the finding of Starr[9] that ballistocardiograms of patients with coronary artery disease are not infrequently abnormal when all other tests of the circulation are normal. Our group has studied a large series of patients with coronary artery disease and compared them with a large group of clinically normal subjects.[10, 11]

It is apparent from figures 1 and 2, and from similar studies by other workers,[12, 13, 14] that there is no specific wave form abnormality indicative of coronary artery disease, but that the group of patients with coronary artery disease have a somewhat higher over-all incidence of abnormal wave forms. Clinically normal subjects may have abnormal records and patients with coronary disease may have normal ones, and one can only speculate upon the meaning of these data. There are two points that seem significant:

(1) Abnormal ballistocardiograms are sufficiently uncommon in both young controls and young patients to make one very suspicious of a young person with an abnormal record. (2) A normal record in older persons perhaps should be regarded with optimism.

The use of stress tests, in our hands, has been disappointing, and the only one that we have encountered that impressively differentiates between normals and patients with coronary artery disease is one based on the effect

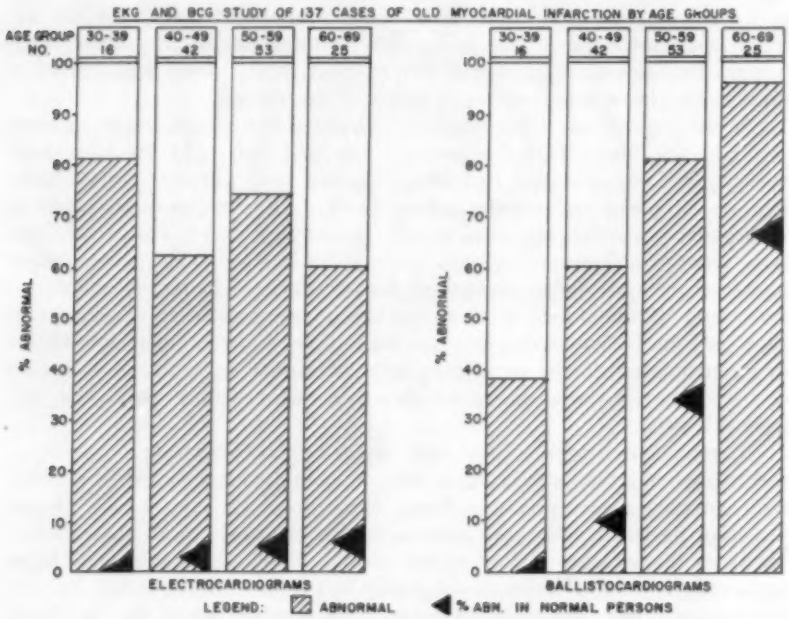

FIG. 1. Electrocardiographic and ballistocardiographic study of 137 cases of old myocardial infarction. The number of patients in each decade is indicated below the age group designation. The black arrow heads represent the values for 369 apparently normal individuals. There is an increasing frequency of ballistocardiographic form abnormality with increasing age in patients with myocardial infarction as well as in normal subjects. Only 38% of patients below the age of 40 had abnormal ballistocardiograms, but the incidence increased to 96% in the seventh decade. (Reproduced by permission of the authors and publisher from Scarborough et al.[10])

of cigarette smoking. This test was first discussed by Dock [15] and studied by Henderson [16] in Starr's laboratory, and has been confirmed and investigated by Davis et al.,[17] of our group.

The solid bars in figure 3 show the incidence of deterioration of the ballistocardiograms of patients with coronary artery disease and normal controls after smoking a cigarette. Whatever the meaning of this: there were nine positive tests in the coronary artery disease group for every one

in the normal group. We will not attempt to discuss here the possible mechanism of this test other than to say that similar ballistocardiographic deterioration followed the sublingual administration of nicotine.

These clinical comparisons of the ballistocardiographic abnormalities of patients and presumably normal controls are admittedly of great interest. However, they are not as yet considered a valid basis for definitive differential diagnosis, a goal which the champions of the technic hope may some day be attained.

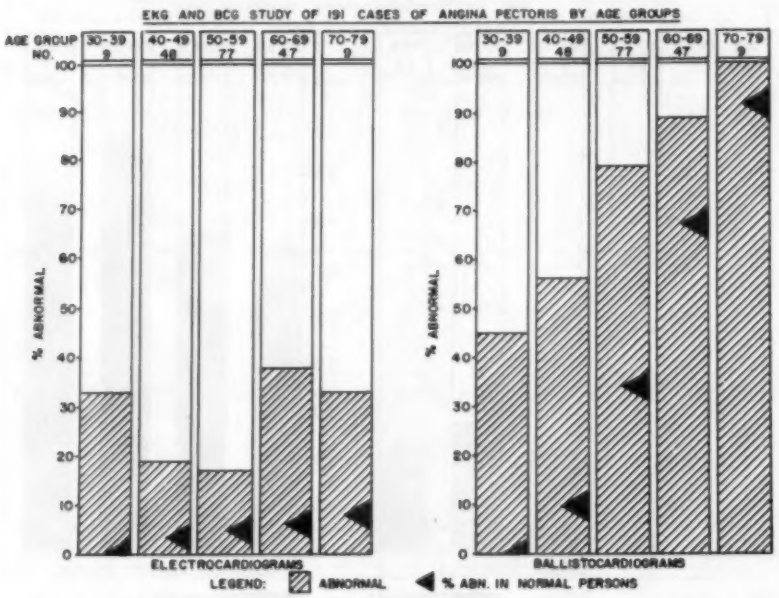

FIG. 2. Results of the electrocardiographic and ballistocardiographic study of 191 cases of angina pectoris. The frequency of abnormal electrocardiograms and ballistocardiograms is significantly higher in the patients with angina pectoris than in normal control subjects, the black arrow heads again indicating the percentage of 369 normal controls having abnormal ballistocardiograms. Note particularly that, as in the infarct group, there is an increase in the frequency of abnormal ballistocardiograms in controls as well as in patients, with aging. (Reproduced by permission of the authors and publisher from Scarborough et al.[10])

This dependence upon empirical studies results from a deficiency of experimental work which intimately relates the form of the ballistocardiogram to the various physiologic events occurring in the circulatory system.

It seems unlikely that the clinical data collected empirically by long-term patient and normal control studies alone will provide the full knowledge we need. This possibility, coupled with our scant understanding of the physio-

logic meaning of ballistic waves, has made some investigators in the field look elsewhere for progress.

It has long been recognized that the physical properties of both the body and the instruments employed to measure the cardiovascular forces generated within the body were such as to make errors in methodology inescapable.

Recently Harrison and Talbot,[18] Burger,[19] von Wittern [20] and others have analyzed current ballistocardiographic methods from both the theoretic physical and experimental standpoints, and have greatly enriched our knowl-

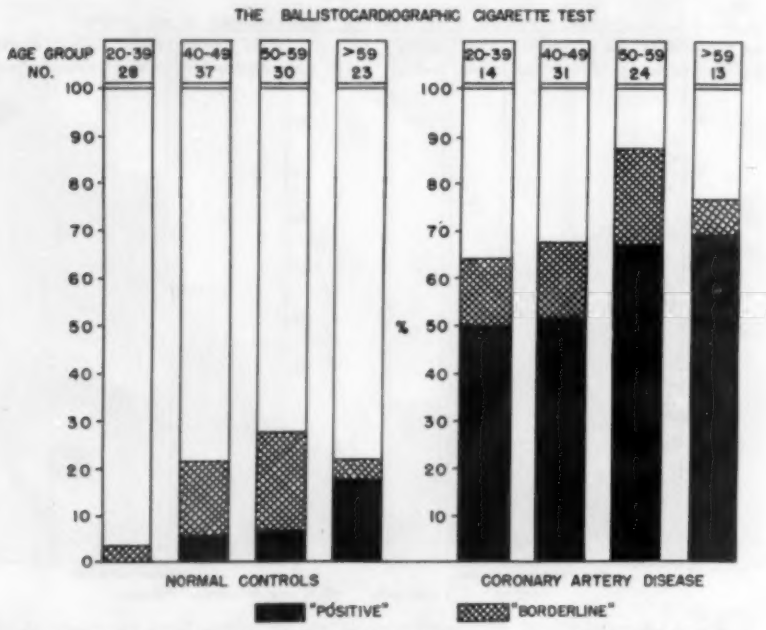

FIG. 3. Incidence of ballistocardiographic abnormalities, after smoking a cigarette, in a group of normal contro' patients and in a group of cases of coronary artery disease. (Reproduced by permission of the authors and publisher from Davis et al.[17])

edge of the mechanical behavior of the human body. These analyses show that the mechanical systems inherent in the Starr high frequency technic, in the Nickerson low frequency technic, and in the direct body pick-up procedures, are all subject to disadvantages bound to lead to distortion and inaccuracy. All of these methods suffer from the fact that the body-platform contacts create oscillations of the body which do not have cardiovascular meaning. These oscillations occur at frequencies which fall in the midst of the ballistocardiographic range and consequently seriously distort the records in both timing and amplitude.

Emerging from these critical studies on methodology is a new and basic concept. In order to obtain the cardiovascular force pattern faithfully, the body has to be supported in such a way that there is no constraint to oppose its motion. Ideally, of course, the body should float in air, as if under the influence of magic. Extraordinarily close approaches to this ideal have recently been achieved. Talbot et al.,[21] of our group, accomplished this by floating the body on a very light raft in a pool of mercury, while Burger [19] and von Wittern,[20] working independently, obtained similar results by

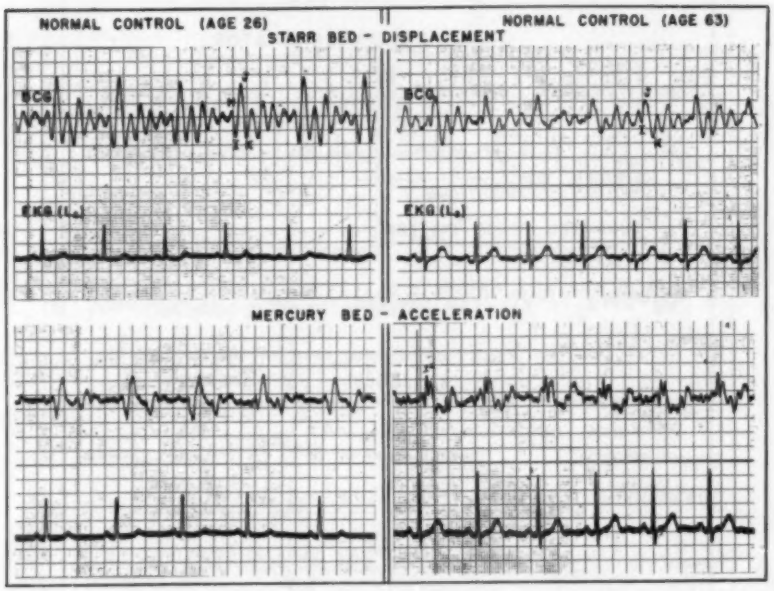

FIG. 4. Comparison of the ballistocardiographic records of two normal control subjects obtained from a Starr bed and a mercury-floated bed. (Reproduced by permission of the authors and publisher from Talbot et al.[21])

placing the body on a very light suspended platform. The records obtained by these newer recording systems are quite different from those more familiar records provided by any of the conventional systems.

On the left of figure 4 you see the two beautifully normal records of a healthy young slender woman; on the right, the clearly abnormal records of a 63 year old, presumably normal control. One can readily see that the mercury bed produces different waves. However, no one knows yet if these records will be any more useful clinically.

In summary, then, these newer methods largely eliminate the artifactual contributions to the ballistocardiogram which arise from the external elastic

coupling between body and supporting surface. They leave the investigator with relatively undistorted records of body motion in response to the internal cardiovascular force over the probable ballistocardiographic frequency spectrum.

What has been said about distortions and their probable connections can be reviewed briefly and emphasized by a schematic diagram (figure 5).

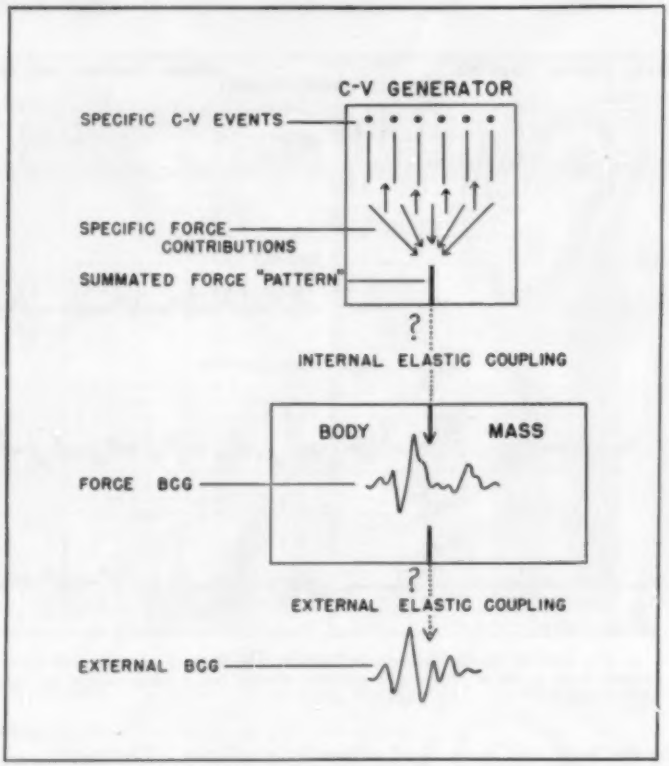

FIG. 5. Schematic diagram illustrating the transmission of cardiac force from the heart to the recording instrument.

This diagram illustrates the complexity and uncertain relationship of the transmission of cardiac force from the heart to the recording instrument. Discrete cardiovascular events, varying in time, magnitude and direction, are summated to form the "cardiovascular force pattern." This, in turn, is modified to an unknown degree by the elastic coupling that connects the heart to the rest of the body and becomes the "force ballistocardiogram"

from the body. This force is again modified by the external coupling of body to bed or floor, and is then transmitted to the instrument to form the external ballistocardiogram. Precise correlation between a specific cardiovascular event and a specific ballistic wave can hardly be expected.

You have doubtless already sensed that my associates and I take a very conservative view regarding the present value of ballistocardiography in clinical practice. We do so because we are enthusiastic about the future of the technic, and we are anxious lest anticipated development and growth

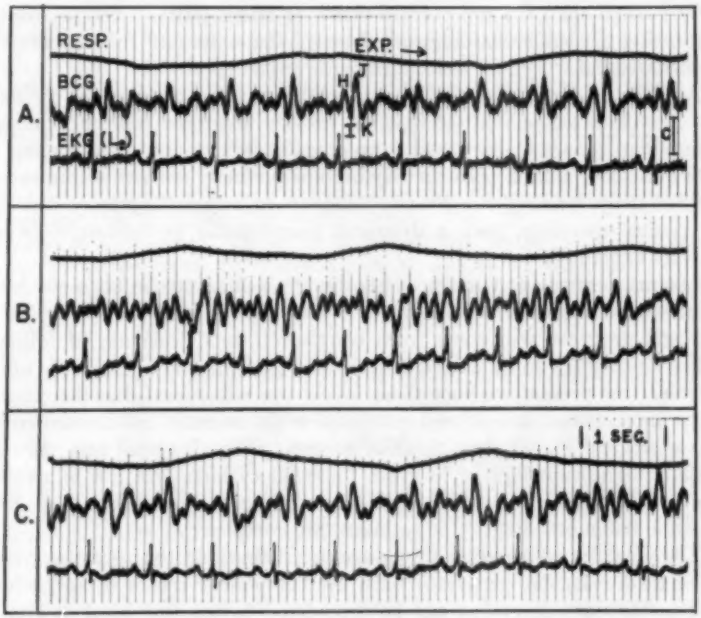

FIG. 6. Ballistocardiographic records of a 62 year old man with a history of angina pectoris. A. Record while at rest. B. Record during an anginal attack. C. Record following relief from nitroglycerin.

of it be stunted by the dissemination of claims based on insufficient evidence.

This audience is made up in part by those who are curious about the ballistocardiograph and are seeking information which will enable them to form opinions, in part by those skeptical of the method, and in part by those who are possibly overly enthusiastic about it. The curious should remain so, watching and observing and reserving firm opinions until after further development has taken place.

As far as the skeptics among you are concerned, before complacently letting you lose all interest I would like you to look at figure 6.

The patient whose records are shown was a 62 year old man reasonably normal to the usual examination. His story undeniably justified the diagnosis of angina pectoris. The top ballistocardiogram, taken when he was at rest, is not normal but contains some quite normal complexes. During the recording of this, while he lay quietly on a Starr-type bed, he complained that he was developing one of his anginal attacks. During the height of the attack the middle tracing was recorded and, at a glance, it can be seen that gross deterioration has taken place. The lower, final tracing was made after nitroglycerin had abolished the attack, and this tracing is actually more nearly normal than the top control one. It seems hard to escape the conclusion that the ballistocardiograph detected the acute and subtle changes in the cardiovascular system associated with angina pectoris.

And finally, let me remind the overenthusiastic who may be critical of our ultraconservative attitude that the grossly abnormal ballistocardiogram of a patient known to have had a myocardial infarct and experiencing frequent attacks of angina pectoris may become perfectly normal within seconds of voluntarily holding the breath. Before ballistocardiography can have real clinical meaning, such a dramatic phenomenon as this must be conclusively explained.

Let me summarize what new knowledge is likely to be acquired by the ballistocardiographer in the future.

Some progress will come from completion and extension of follow-up studies already begun by us and others upon patients and presumably normal controls. At present we hope these follow-ups will reveal that the coronary artery circulations of normal controls with normal ballistocardiograms remain efficient longer than those of controls with abnormal records. Statistically significant figures to make these hopes facts will not be available until such long-term studies, utilizing the conventional and the newer aperiodic ballistocardiographic technics, are completed.

The ideal line of progress should connect definitively the physiologic events in the cardiovascular generator with the component waves of as faithful a force ballistocardiogram as can be recorded. When this ideal is attained, then ballistocardiography will provide not only information upon the clinical cardiovascular efficiency not obtainable by other means but also information which is desperately needed by the clinician to guide him both in his therapy and in his predictions of the outcome of his patient's ills.

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THE SUBMERSION SYNDROME *

By Myron Saline, M.D., and George L. Baum, M.D., F.A.C.P.,
Coral Gables, Florida

The roentgenographic finding of transitory pulmonary densities observed in a patient recovering from an episode of submersion is the basis for this report. The relative paucity of reports in the literature relating to this not unusual condition is of considerable interest. The clinical records of 26 such cases admitted to three hospitals in the Greater Miami area during the period from 1947 to 1953 are reviewed. The purpose of this report is to correlate the symptomatology with the presence of asphyxia rather than with that of aspiration. The salient findings in these 26 patients are summarized in table 1. One case will be presented in detail.

Table 1

Total Number of Patients Studied		26
Leukocytosis with shift to left	22	
Pulmonary manifestations	19	
Basilar râles only	16	
Pulmonary edema	3	
Cyanosis	16	
Tachypnea	16	
Neurologic symptoms	13	
Evidence of shock	8	
Fever	7	
Gastrointestinal symptoms	5	
Average duration of hospitalization	2.5 days	
Associated diagnosis	7	
Hypertensive heart disease	2	
Multiple contusions	2	
Bronchiectasis	1	
Barbiturate intoxication	1	
Coronary insufficiency and myocardial infarction	1	

The average hospital stay of two and one-half days in this series indicates a rather benign transitory process. In no instance was a temperature elevation of above 101° F. recorded, nor was the duration of the febrile episode over three days in any case. Neurologic manifestations included transitory restlessness, vertigo, confusion and unconsciousness, and were present in 50 per cent of the cases studied. Gastrointestinal symptomatology consisted of abdominal distention, nausea and vomiting.

Roentgenographic study of the chest was performed in 11 instances. Five were interpreted as presenting evidences of pulmonary congestion or edema. Nineteen patients showed clinical evidences of pulmonary edema and congestion. Sixteen were described as being dyspneic and cyanotic.

* Received for publication March 17, 1954.
From the Medical Service, Veterans Administration Hospital, Coral Gables, Florida.

Electrocardiographic evidences of auricular fibrillation and coronary insufficiency, progressing to those of acute myocardial infarction, were present in one patient. The duration of the necessarily prolonged hospitalization in this instance was excluded in calculating the average for this series.

Case Report

On August 16, 1953, a 21 year old white male was submerged in an automobile for a period estimated by eyewitnesses to be "five to 10 minutes." He was rushed to a local hospital, where he was found to be conscious, although cyanotic and expectorating frothy red sputum. Respirations were described as delayed and irregular. There was emesis of brownish material. Blood pressure was recorded as 120/80 mm. of Hg. One hundred per cent oxygen was administered continuously, with clearing of the cyanosis. The patient was transferred to the Coral Gables Veterans Administration Hospital, arriving about three hours after the submersion episode. At this time there was clinical evidence of shock, with a blood pressure of 90/70 mm. of Hg and a heart rate of 120/minute. Cyanosis was again present. One hundred per cent oxygen inhalations, at first by B.L.B. mask followed by four hours of exhalation positive pressure administration, and then by nasal catheter, were administered. Cyanosis rapidly cleared. One unit of plasma and 2 L. of 5 per cent glucose in distilled water were given intravenously and the blood pressure returned to normal.

Intermittent positive pressure breathing (IPPB-I) was employed during the second and third hospital days. This was instituted because of radiographic evidence of bilateral pulmonary edema (figure 1) obtained shortly after admission. Other therapy included the administration of oxytetracycline (Terramycin) and streptomycin.

Bronchoscopy performed 30 hours after admission failed to reveal any evidence of fluid, secretion or obstruction. Electrocardiogram at this time revealed no abnormalities. Routine laboratory work on the second hospital day indicated a white blood count of 14,700 mm.^{3}, with 80 per cent polymorphonuclears, 10 per cent band forms, 9 per cent lymphocytes and 1 per cent monocytes.

Temperature ranged from 99° to 100° F. for three days. Blurred vision and headache were troublesome and did not respond to symptomatic treatment. Examination of the spinal fluid, including manometrics, was within normal limits. These symptoms persisted until the date of discharge (August 24, 1953).

A chest x-ray on the third hospital day revealed practically complete clearing of the previously observed bilateral pulmonary densities (figure 2).

Discussion

The clinical, radiographic and hematologic changes described in the 26 patients recovering from submersion are related solely to the effects of asphyxia rather than to those of aspiration. Aspiration pneumonia can be eliminated because of the short duration, lack of significant pyrexia, and transitory pulmonary manifestations.

The symptomatology is dependent upon the degree of hypoxia.[1] When it is slight, there may be a feeling of well being and power. As the hypoxia increases there are emotional instability and loss of judgment. Muscular incoördination, deterioration of vision and memory loss ensue. Hyperpnea and a feeling of lassitude or extreme weakness may occur. In severe states, convulsions followed by unconsciousness and death are noted.

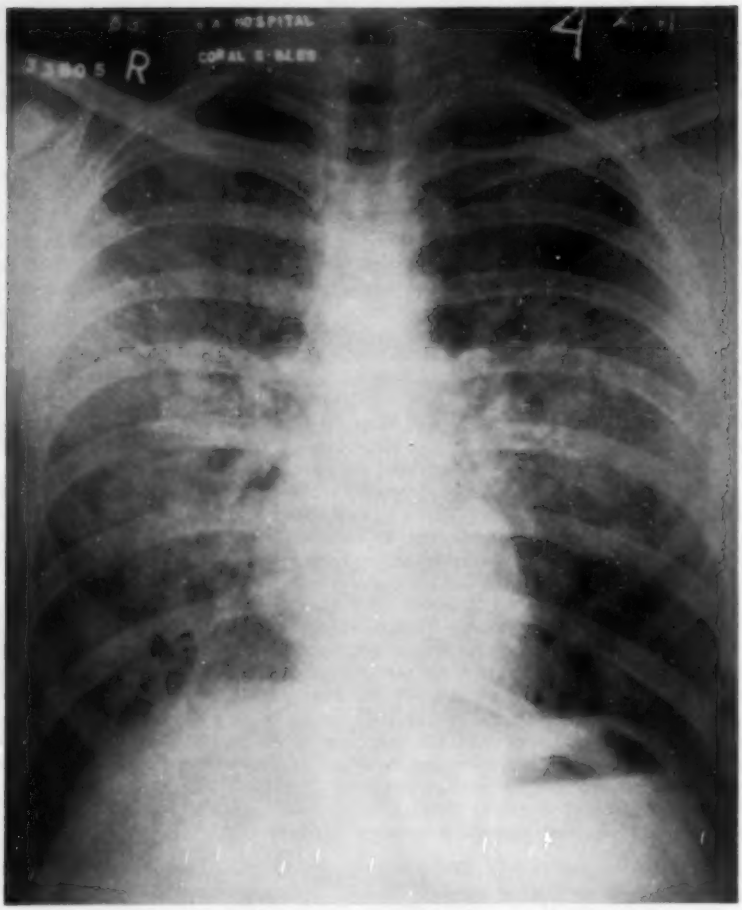

FIG. 1. Bilateral pulmonary densities compatible with pulmonary edema.

The effects of oxygen lack on the digestive tract and in the production of shock are likewise well known.

Experimentally, the inhalation of decreased percentages of oxygen has been shown to produce a rise in right ventricular output. This rise is greater than the increased pulmonary vascular resistance. The result is a redistribution of blood in the pulmonary vascular bed.[2, 3] There is also increased permeability of pulmonary capillaries in the presence of inadequate lymphatic drainage.[4] The effect is further decrease in gaseous exchange.

The interaction of these forces leads to the production of pulmonary

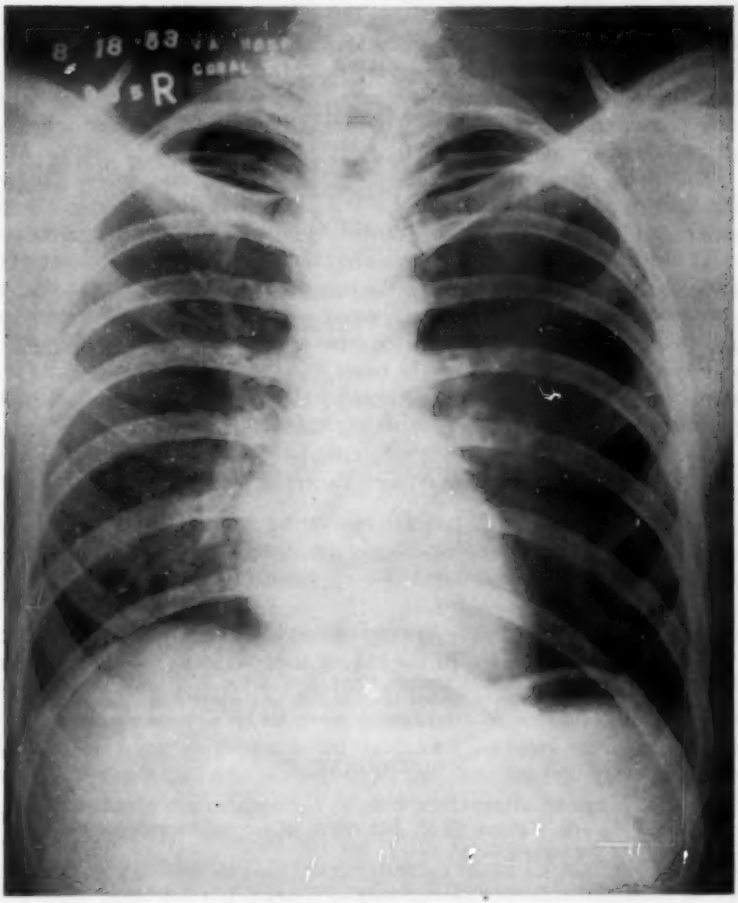

FIG. 2. Practically complete clearing of previously described densities.

edema. This was certainly present in the case reported above. Either pulmonary edema or congestive changes were present in 19 of the 26 reported cases.

The radiographic changes in the lungs after submersion have been described by Romagosa et al.[5] as being due to acute edema which is rapidly absorbed.

Experimentally, the outcome in the drowned animal has been shown to be related to the ionic content of the water. In survived animals there is little or no water in the lungs and no change in blood electrolyte content.[6]

In our case there was no bronchoscopic evidence of aspiration, although it should be noted that this endoscopic procedure was performed 30 hours after admission. Salt water drowning in animals and in humans is associated with the production of pulmonary edema and hemoconcentration, while fresh water drowning results in death with hemodilution.[7, 8] These changes are ascribed to water passing into the lungs.

The water in which the patient reported herein was submerged was submitted to analysis. There was a low ionic content: chloride, 100 mg. per cent, and sodium, 1.7 mg. per cent. Although this patient was the only one of the 26 not submerged in sea water, the clinical findings did not differ materially from those exhibited by the others. It is our conclusion that the hypertonicity or hypotonicity of the water is of little import, in view of the lack of evidence of aspiration in those recovering from submersion.

The elevation of the leukocyte count deserves mention. It is felt that this occurs in anoxic states as a nonspecific effect of stress,[9] with the production of a neutrophilia associated with a lymphopenia.

Summary and Conclusions

The relevant data in 26 patients recovering from submersion were presented. The various manifestations have been shown to be related to anoxia, without evidence of aspiration of water into the lungs.

Acknowledgment

We are grateful to Dr. David Nathan, Chief of Medicine, Mount Sinai Hospital, Miami Beach, Florida, and to Dr. Donald Stannus, Chief of Medicine, St. Francis Hospital, Miami Beach, Florida, for permission to review their records and report data obtained from their cases. We are also indebted to Mrs. Catherine Ashley for her technical assistance.

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SERUM CHOLINESTERASE IN HEPATIC AND NEOPLASTIC DISEASES: A PRELIMINARY REPORT *

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Introduction

The purpose of this preliminary report is to describe a new colorimetric method to determine serum cholinesterase activity. The results of this enzyme activity for 110 normal patients, 57 patients with liver disease of multiple etiology and 20 whose liver dysfunction was presumably due to metastatic disease are presented. The possible usefulness of serum cholinesterase as a test of parenchymal liver disease is discussed in relation to the other standard liver function tests.

Methods

The method used in determining serum cholinesterase is an adaptation of that originally developed by Michel,[1] but employs a colorimeter rather than potentiometer for measurements. The procedure can be readily carried out using equipment available in most present-day clinical chemical laboratories.

This method measures colorimetrically the acetic acid liberated when cholinesterase present in serum hydrolyzes acetyl choline added to serum in known amount and under controlled conditions. Phenol red is used as the indicator. The reaction is carried out in a barbiturate buffer system. The ΔpH is measured by comparing galvanometer readings against a readily reproducible standard curve prepared with barbiturate buffers.[2]

The barbiturate buffer is prepared by mixing 82.3 ml. of a sodium barbiturate stock solution (prepared by dissolving 10.30 gm. of sodium barbital in 500 ml. distilled water) with 17.7 ml. of 0.1N HCl. This buffer will have a pH of 8.4. The phenol red indicator solution is made by dissolving 0.050 gm. phenol red in 10 ml. of 0.1N NaOH and diluting to 200 ml. with distilled water. Acetylcholine chloride is used as the substrate and is prepared by dissolving 3.5 gm. in 100 ml. of distilled water.

A standard curve is prepared by adding 2.0 ml. barbiturate buffer [2] in the range of pH 7 to 8.6 to 8.0 ml. distilled water, followed by 0.15 ml. phenol red indicator. These solutions are read in a colorimeter with a 535

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mu filter with water for the blank setting. The curve is linear in the range of pH 7.2 to 8.5.

One tube is used for the initial pH, another for the final pH, and a third as a blank setting to compensate for the color in the serum. Tube one is prepared by adding 2.0 ml. of barbiturate buffer of pH 8.4 to 1.0 ml. of acetylcholine chloride (35 mg.) and 0.1 ml. serum. Tubes two and three originally contain 2.0 ml. barbiturate buffer of pH 8.4, 1.0 ml. distilled water and 0.1 ml. serum.

All tubes are incubated at 37° C., and final colorimetric readings should be made after exactly 120 minutes. A few minutes before the expiration of this period 7.0 ml. distilled water are added to each tube and 0.15 ml. phenol red indicator solution is placed in tubes one and two. With tube

TABLE 1

Comparison of Cholinesterase Activity of Colorimetric Method with Michaelis Buffer and Michel Potentiometric Method

Potentiometric pH/2 hrs.	Colorimetric pH/2 hrs.	Michel Potentiometric pH/hrs.	Increased by Michel Method Per Cent
0.44	0.44	0.49	11
0.58	0.63	0.67	7
0.60	0.58	0.66	14
	0.35	0.40	14
	0.40	0.45	12
	0.38	0.45	18
0.51	0.50	0.58	16
0.58	0.55	0.62	13
0.56	0.48	0.54	13
0.54	0.59	0.73	24
0.52	0.49	0.58	18
0.56	0.55	0.69	25
0.24	0.21	0.24	14
0.45	0.39	0.50	28
0.66	0.64	0.73	14
		Average	16 ± 4

three as the blank, tubes one and two are read in a colorimeter with a 535 mu filter and the result is compared with the standard curve. The ΔpH is calculated by subtracting the final pH of tube one from the initial pH of tube two. All reference to pH changes in this work done by the colorimeter method means ΔpH/2 hours.

In order to compare the sensitivity of the colorimetric procedure with the electrometric method of determining pH values, colorimetric and potentiometric readings were determined simultaneously and were found to check within 0.03 pH units as indicated in table 1. The colorimetric method was also compared with Michel's method, the values being listed in column 3 of table 1. The results by Michel's method average 16 per cent higher. This is accounted for by the fact that the Michel buffer is more dilute than the Michaelis buffer. These data would suggest that the simpler colori-

metric method gives constant readings for serum cholinesterase. It would appear that the limit of accuracy over a range of enzyme activity in various sera is comparable to that obtained in Michel's procedure. This method has been found to be easily reproducible, duplicate readings checking within 0.03 pH units. Promptly frozen sera have been found to show reproducible cholinesterase levels at monthly intervals for several months.

In addition to a determination of serum cholinesterase activity, the following routine liver function studies were done: serum bilirubin,[3, 4] alkaline phosphatase,[5] thymol turbidity,[6, 7] cephalin cholesterol flocculation,[8] total serum protein with albumin-globulin ratio,[9] and cholesterol and cholesterol esters.[10]

Results

The frequency distribution of the serum cholinesterase levels in 110 normal patients is plotted in figure 1, and the values of serum cholinesterase in 57 other patients are tabulated in tables 2 and 3. In table 4 the results of the other liver function tests are listed. In tables 5, 6, 7 and 8 the comparative sensitivity of serum cholinesterase in relation to other tests of liver function is presented.

The patients were divided into two large groups, those with primary liver disease including hepatitis, cirrhosis, and primary carcinoma of the

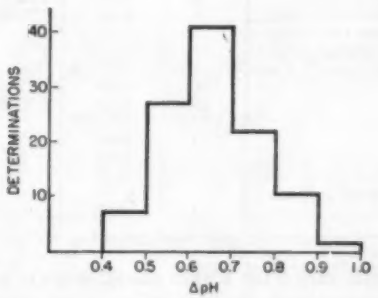

Fig 1.

Table 2

Serum Cholinesterase Activity
Normal = 0.66 ± 0.22 pH Units

	Patients	Per Cent Normal	Per Cent Abnormal
Disease primary in the hepatobiliary system	20	40	60
Liver disease secondary to primary disease in some other organ	37	35	65
Total	57	37	63

liver, and those with involvement of the liver as a complication of primary disease located in some other organ. The latter group included such patients as those with metastatic carcinoma or lymphoma, as well as those with obstructive jaundice.

The ages of the 110 healthy people varied from 18 to 65. Sex distribution was about equal. It has been previously shown that sex does not affect the serum cholinesterase values, whereas young infants and children may have lower values than adults.[11] The normal range of enzyme activity varied from 0.42 ΔpH to 0.93 ΔpH, with a mean of 0.66 ΔpH. In this

TABLE 3

The Serum Cholinesterase Activity in Primary and Metastatic Liver Disease

Diagnosis	Patients	Average Δ pH	Range Δ pH	Per Cent Normal	Per Cent Abnormal
Normal	110	0.66±0.22	0.42–0.22		
Patients with primary disease in the hepatobiliary system:					
Acute:					
Homologous serum jaundice:					
Acute phase	3	0.39	0.36–0.42		100
Convalescent phase	2	0.82	0.80–0.84	100	
Chronic:					
Alcoholism—fatty liver	1	0.52			
Chronic hepatitis	2	0.44	0.41–0.46	50	50
Laennec's cirrhosis	8	0.40	0.25–0.57	37.5	62.5
Carcinoma of hepatobiliary system	4	0.34	0.21–0.48	25	75
Patients with liver disease secondary to primary disease in some other organ:					
Metastatic carcinoma	20	0.45	0.27–0.72	40	60
Lymphoma	13	0.44	0.20–0.80	30	70
Obstructive jaundice:					
Uncomplicated	1	0.66			
Complicated	1	0.42			
Cooley's anemia	1	0.39			
Hepatosplenomegaly (cause undetermined)	1	0.37			

laboratory the normal range for serum cholinesterase activity has been defined as the mean value plus or minus two standard deviations from the mean, i.e., 0.66 ± 0.22 ΔpH.

Patients with Primary Liver Disease (Group I): In three patients (cases 1, 2, 3) acutely ill with homologous serum jaundice, the cholinesterase ranged from 0.36 to 0.47 ΔpH, which is comparable to results previously reported.[14, 15] The other liver function tests done demonstrated abnormalities most evident when measured by the thymol turbidity and cephalin flocculation reactions. In these same three patients the cephalin flocculation was 4 plus in 48 hours, the thymol turbidity 9.2 to 27.6 units and the bilirubin 7.1 mg. per cent to 16.8 mg. per cent. The serum globulin was high in one patient and high normal in another, and in both the albumin was

TABLE 4
Primary Hepatobiliary System Disease

Patient	Diagnosis	Cholinesterase, 0.66±0.22 pH/hr.	Bilirubin, 1.0 mg. %	Alkaline Phosphatase, 2.5–8.0 S.J.R. Units	Cephalin Flocculation, 2+48 hrs. Units	Thymol Turbidity, 5 Units	Protein, 5.5–8.8 gm. %	Albumin, 3.0–5.5 gm. %	Globulin, 1.8–3.0 gm. %	Inorganic Phosphorus, 2.5–4.5 gm. %	Total Cholesterol, 150–250 mg. %	Cholesterol Esters, 65–75%
1.*	Homologous serum jaundice Acute phase	0.42	16.8	15.9	4	27.6	6.8	3.1	3.7	4.2	282	113
2.	Homologous serum jaundice Acute phase	0.36	7.1	10.0	4	20.3	5.5	2.5	3.0		195	115
3.*	Homologous serum jaundice Acute phase	0.40	14.68	5.2	4	9.2				3.2	213	148
4.*	Homologous serum jaundice Convalescent phase	0.84		7.8	2	11.9	7.1	3.5	3.6	4.2	304	152
5.*	Homologous serum jaundice Convalescent phase	0.80	1.40	7.6	3	9.3				3.9	217	126
6.	Chronic alcoholism	0.52	0.40	10.1	Neg.	5	6.5	4.0	2.5	3.9	290	225
7.	Chronic hepatitis	0.41	0.40	4.9	Neg.	5.2	6.6	4.1	2.5	4.7	201	168
8.*	Chronic hepatitis	0.46	1.15	5.4	1	5				4.0	304	229
9.	Laennec's cirrhosis	0.34	2.2	8.9	4					3.7	240	156
10.	Laennec's cirrhosis	0.57	1.1	6.7	Neg.	5				3.7	251	164
11.*	Laennec's cirrhosis	0.41	10.74	58.4	Neg.					4.0	209	114
12.	Laennec's cirrhosis	0.44	1.60		3	5.22	7.70	3.94	3.96		479	314
13.	Laennec's cirrhosis	0.25	3.59	16.0	4	4.88	5.70			4.0		
14.	Laennec's cirrhosis	0.40	1.04		2	0.30	5.50	2.75	2.25	3.4		
15.	Laennec's cirrhosis	0.32	4.0	12.0	4	13.7	6.7	1.9	4.8	3.6	172	113
16.*	Laennec's cirrhosis	0.44	1.8	18.9	3	5	6.0	2.4	3.6	3.4	145	100
17.	Carcinoma of hepatobiliary system	0.39	18.9	51.5	3	7.2	8.3	2.6	5.7	2.9	484	251
18.	Carcinoma of hepatobiliary system	0.48	0.55	30.1	Neg.		6.8	3.4	3.4		217	152
19.	Carcinoma of hepatobiliary system	0.21	11.6	18.3	4	13.5	5.6			4.7	179	37
20.	Carcinoma of hepatobiliary system	0.27	20.0									

* Patients hospitalized at Memorial Center.

TABLE 4—*Continued*

Liver Disease Secondary to Primary Disease in Some Other Organ

Patient	Diagnosis	Cholinesterase, 0.66±0.22 pH/hr.	Bilirubin, 1.0 mg. %	Alkaline Phosphatase, 2.5–8.0 S.J.R. Units	Cephalin Flocculation, 2+48 hrs. Units	Thymol Turbidity, 5 Units	Protein, 5.5–8.8 gm. %	Albumin, 3.0–5.5 gm. %	Globulin, 1.8–3.0 gm. %	Inorganic Phosphorus, 2.5–4.5 gm. %	Total Cholesterol, 150–250 mg. %	Cholesterol Esters, 65–75%
21.	Metastatic carcinoma	0.28	0.45	12.4		5	6.1	2.4	3.7	8.4	185	107
22.	Metastatic carcinoma	0.42	0.40	11.1	Neg.	5	6.4	3.3	3.1	3.5	290	145
23.*	Metastatic carcinoma	0.39	0.25		Neg.		2.6					
24.*	Metastatic carcinoma	0.40		7.9	Neg.	5				2.0		
25.	Metastatic carcinoma	0.42	0.55	40.6	Neg.	5	6.0	3.4	2.6	3.9	159	107
26.*	Metastatic carcinoma	0.34	6.6		3	5	5.9	3.0	2.9		138	49
27.*	Metastatic carcinoma	0.41	18.6	14.4	Neg.	5	6.2	2.7	3.5	3.1	208	149
28.	Metastatic carcinoma	0.27	8.9		Neg.	5	5.8	3.3	2.5	3.5	231	60
29.	Metastatic carcinoma	0.50		11.1	2	5.7				4.5	274	
30.*	Metastatic carcinoma	0.38	20.4	38.1	Neg.		6.2	3.1	3.1	4.4		
31.	Metastatic carcinoma	0.48	0.55	7.5	Neg.		5.4	3.1	2.3	4.5		
32.	Metastatic carcinoma	0.42										
33.	Metastatic carcinoma	0.38										
34.*	Metastatic carcinoma	0.48	0.50	9.0	Neg.		6.27	3.4			137	
35.*	Metastatic carcinoma	0.59	1.68	27.6		1.20	5.50	3.32		4.0	268	177
36.*	Metastatic carcinoma	0.49		40.8	Neg.	3.66					361	
37.*	Metastatic carcinoma	0.36	1.75	2.0	2		7.3	3.5	3.8	3.7	182	122
38.*	Metastatic carcinoma	0.54	2.80		2	5	6.1	3.1	3.0	3.8	138	
39.	Metastatic carcinoma	0.60	0.43	9.2						4.4		
40.	Metastatic carcinoma	0.72		5.90						4.5		
41.*	Lymphoma	0.33										
42.	Lymphoma	0.67	0.20	6.5	2	7.0						
43.*	Lymphoma	0.50	0.35	9.8	Neg.	5	5.3	3.4	1.9	4.2	219	87
44.*	Lymphoma	0.41	1.1	5.5	3	6.1	6.5	3.3	3.2	4.9	156	71
45.	Lymphoma	0.38	0.40	5.6	Neg.	5	5.9	3.9	2.0	3.7	208	
46.*	Lymphoma	0.35	18.6		Neg.	5	6.5	3.0	3.5	3.0	252	66.0
47.*	Lymphoma	0.33	0.40	13.4	Neg.	5	5.5	2.8	2.7	3.9	114	
48.*	Lymphoma	0.20	1.25	7.4		5	5.4	3.1	2.3	3.9	172	118
49.	Lymphoma	0.37										
50.	Lymphoma	0.32										
51.	Lymphoma	0.64		10.9	2	9.7	5.8	3.6	2.2	2.7	185	136
52.*	Lymphoma	0.80		7.8	Neg.	8.0	7.7	4.4	3.3	3.7	430	323
53.	Lymphoma	0.38			Neg.	5	6.5	4.2	2.3		248	182
54.	Obstructive jaundice Uncomplicated	0.66	3.93	38.8		5	6.5	3.6	2.9	4.7	295	159
55.	Obstructive jaundice Complicated	0.42	2.4	8.40	Neg.	5	5.1	2.8	2.3	3.8	172	110
56.*	Cooley's anemia	0.39	5.25	7.6		5	7.7	4.1	3.6	3.8	122	82
57.	Hepatosplenomegaly (cause undetermined)	0.37										

TABLE 5

Comparative Sensitivity of Cholinesterase Patients with Metastatic Carcinoma

	Cholinesterase, 0.66 ±0.22 pH/hr.	Bilirubin, 1.0 mg. %	Alkaline Phosphatase, 2.5–8.0 S.J.R. Units	Cephalin Flocculation, 2+48 hrs. Units	Thymol Turbidity, <5 Units	Protein, 5.5–8.8 gm. %	Albumin, 3.0–5.5 gm. %	Globulin, 1.8–3.0 gm. %	Inorganic Phosphorus, 2.5–4.5 gm. %	Total Cholesterol, 150–250 mg. %
Normal	8	6	3	13	11	12	10	5	5	3
Abnormal	12	7	9	1	1	1	2	5	7	6

TABLE 6

Comparative Sensitivity of Cholinesterase Patients with Metastatic Carcinoma

	Cholinesterase, 0.66 ±0.22 pH/hr.	Bilirubin, 1.0 mg. %	Alkaline Phosphatase, 2.5–8.0 S.J.R. Units	Cephalin Flocculation, 2+48 hrs. Units	Thymol Turbidity, <5 Units	Protein, 5.5–8.8 gm. %	Albumin, 3.0–5.5 gm. %	Globulin, 1.8–3.0 gm. %	Inorganic Phosphorus, 2.5–4.5 gm. %	Total Cholesterol, 150–250 mg. %
		Normals								
Normal	8	2	1	5	3	3	4	2	1	0
		Abnormals								
		2	4	0	1	0	0	0	4	2
		Normals								
Abnormal	12	4	2	8	8	8	6	3	4	3
		Abnormals								
		5	5	1	0	1	2	5	3	4

TABLE 7

Comparative Sensitivity of Cholinesterase Patients with Lymphoma

	Cholinesterase, 0.66±0.22 pH/hr.	Bilirubin, 1.0 mg. %	Alkaline Phosphatase, 2.5–8.0 S.J.R. Units	Cephalin Flocculation, 2+48 hrs. Units	Thymol Turbidity, <5 Units	Protein, 5.5–8.8 gm. %	Albumin, 3.0–5.5 gm. %	Globulin, 1.8–3.0 gm. %	Inorganic Phosphorus, 2.5–4.5 gm. %	Total Cholesterol, 150–250 mg. %
Normal	4	4	5	8	7	7	8	6	5	4
Abnormal	9	3	4	1	3	2	1	3	4	3

TABLE 8

Comparative Sensitivity of Cholinesterase Patients with Lymphoma

	Cholinesterase, 0.66±0.22 pH/hr.	Bilirubin, 1.0 mg. %	Alkaline Phosphatase, 2.5–8.0 S.J.R. Units	Cephalin Flocculation, 2+48 hrs. Units	Thymol Turbidity, <5 Units	Protein, 5.5–8.8 gm. %	Albumin, 3.0–5.5 gm. %	Globulin, 1.8–3.0 gm. %	Inorganic Phosphorus, 2.5–4.5 gm. %	Total Cholesterol, 150–250 mg. %
		Normals								
Normal	4	2	2	4	1	2	3	2	2	2
		Abnormals								
		0	2	0	3	1	0	1	1	1
		Normals								
Abnormal	9	2	3	4	5	5	5	4	3	2
		Abnormals								
		3	1	1	1	1	1	2	3	2

depressed. Protein determinations were not done in the third patient. The alkaline phosphatase was 15.9 units and 10.0 units, respectively, in the two patients, being normal in the patient whose protein level was not done.

In the convalescent phase of hepatitis normal values were seen in two instances (cases 4, 5), whereas the thymol turbidity test was still abnormal.

In cases 6, 8, 9, 11, 13, 14 and 15, with chronic liver disease, the results were variable. Case 7 (chronic hepatitis) showed a moderately low level (0.41 ΔpH), whereas the other tests of liver function were not remarkably altered. This patient, a nurse in a liver clinic, complained of moderate fatigability at the time of the determination. In three instances of Laennec's cirrhosis (cases 10, 12, 16), the cholinesterase activity was within normal limits, yet other tests of liver function showed abnormalities. Inspection of the other liver function tests reveals that there was no apparent constant correlation between the degree of derangement of the various liver function tests and the serum cholinesterase determination. Cases 17 and 19 with carcinoma of the liver, and one (case 20) with adenocarcinoma of the bile ducts, definitely had low enzyme activity, the values being 0.21 ΔpH to 0.39 ΔpH, whereas case 19, with adenocarcinoma of the bile ducts, was low normal. In 20 patients with metastatic carcinoma of the liver (cases 21 through 40), low values were found in 12 (60 per cent), the range being 0.26 ΔpH to 0.42 ΔpH. Although the number of cases is small, it appears that seriously ill patients with extensive metastases tended to have lower levels. It is noted that normal cholinesterase levels were found in eight of the 20 patients with metastatic carcinoma of the liver. In table 5 the relationship between the normal and abnormal in various liver function tests is noted. Not all liver function tests were done in all patients; therefore, in table 6 a further effort was made to show the number of normal and abnormal results of different tests compared to normal and abnormal results of the cholinesterase activity. Of the eight patients with normal cholinesterase values, two had normal bilirubin levels and two had elevated levels. Of 12 patients with low cholinesterase levels, four had normal bilirubin values and five had elevated levels of bilirubin in their serum. It is of interest that, of these same 12 patients, eight had normal cephalin flocculation, thymol turbidity and total serum protein levels. Four patients were found to have normal cholesterol levels. Abnormal alkaline phosphatase was found in four instances of five determinations out of eight patients with normal cholinesterase enzyme activity. Of the 12 patients with low cholinesterase enzyme activity, five instances of abnormal phosphatase were seen in the seven determinations that were carried out.

Thirteen patients with lymphoma (cases 41 through 53) with clinical evidence of active disease showed serum cholinesterase values of 0.20 ΔpH to 0.80 ΔpH, being low in nine instances. Of these nine patients, three had normal alkaline phosphatase, four had normal cephalin flocculations, and five each had normal thymol turbidity, total serum proteins and serum albumin

levels. In tables 7 and 8 the comparative sensitivity of the various liver function tests is tabulated.

A jaundiced patient with a stone in the common duct had a normal value (0.66 ΔpH), whereas a patient with prolonged jaundice due to carcinoma of the head of the pancreas had a moderately low value (0.42 ΔpH). The cholinesterase was 0.39 ΔpH in a patient with Cooley's anemia.

Occasionally when the other liver function tests have not been greatly altered, the serum cholinesterase has been low and has been a useful guide to the clinician in planning treatment. Serum cholinesterase activity may prove helpful in interpreting the values of other liver function tests, particularly in patients with parenchymal liver disease and intrahepatic biliary obstruction, where elevated alkaline phosphatase levels suggest obstructive jaundice. This is illustrated by the following case summary (case 2, table 4).

Case Report

A 70 year old white male was admitted to Memorial Center the latter part of April, 1951, for an abdominoperineal resection for carcinoma of the rectum which had caused rectal bleeding. The patient underwent surgery and did well until the end of the first postoperative week, at which time icterus developed. Liver function tests as recorded under case 11 in table 3 showed an elevated bilirubin and alkaline phosphatase and a normal cephalin flocculation. Repeated determinations confirmed this. The cholinesterase was 0.41 ΔpH units. The clinical impression was that this was an obstructive jaundice, probably due to a stone in the common duct. Laparotomy revealed the presence of cirrhosis. This suggests that cholinesterase activity as a complementary liver function test in the face of an elevated alkaline phosphatase in the presence of jaundice may be helpful in the differential diagnosis between surgical and nonsurgical jaundice.

Discussion

Most investigators have found the serum cholinesterase to be decreased in hepatocellular liver disease,[12, 13, 14] normal in uncomplicated instances of obstructive jaundice, and variable in patients with chronic liver disease. Vorhaus [15] reported that, of two patients with metastatic carcinoma involving the liver, one had a low and the other a normal cholinesterase level.

Vorhaus has brought forth evidence that serum cholinesterase is produced in the liver, that patients with liver disease have an impaired ability to regenerate cholinesterase, and that liver cholinesterase parallels serum cholinesterase. In addition, some investigators have observed a relationship between serum albumin levels and cholinesterase activity,[18] although this may not be evident from single cholinesterase or serum albumin determinations. It is stated that cholinesterase is composed largely of an alpha globulin.[16]

Figure 2 demonstrates the relation between serum cholinesterase activity and level of serum albumin. It is seen that no constant correlation is found,

although a normal cholinesterase activity is generally found only in association with a normal serum albumin level, whereas the reverse is not a constant finding. Low albumin levels were generally associated with low enzyme activity.

Vorhaus has reported the depression of serum cholinesterase levels [18] in normal individuals but not in cirrhotics following the intravenous administration of albumin. In general, it is believed that serum cholinesterase activity is a reflection of the efficiency of hepatocellular protein synthesis.[17]

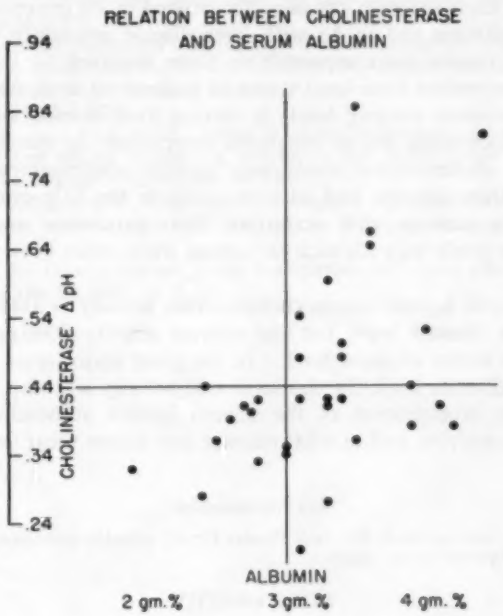

FIG. 2.

Low serum cholinesterase levels have also been reported in cases of anemia and infection.[14] The exact significance is not clearly known. Low levels have been found in patients with acute parenchymal liver disease. The levels have varied in cirrhotics. In patients with widespread metastatic carcinoma with metastases to the liver, low levels have generally been found. In cases of lymphoma with liver involvement, low levels have been consistently seen. In general, patients with extensive liver disease have lower levels than those with less involvement. The serum cholinesterase levels have progressed toward normal with treatment and clinical improvement of some patients with lymphoma.

Conclusions

1. A simple, accurate, easily reproducible colorimetric method for serum cholinesterase activity comparing favorably with Michel's potentiometric method for serum cholinesterase has been described. The method is relatively simple and can be readily performed in any clinical laboratory equipped with a colorimeter.

2. Normal cholinesterase values using this method are 0.66 ± 0.22 ΔpH units.

3. Serum cholinesterase has been determined in 20 patients with parenchymal liver disease and in 33 with liver disease secondary to metastatic cancer. The results are comparable to those reported by other workers. In general, low values have been found in patients ill with acute parenchymatous liver disease, varying levels in chronic liver disease, and low values in metastatic carcinoma and in lymphoma complicated by spread to the liver.

4. Serum cholinesterase levels may provide confirmatory evidence of parenchymal liver damage, and, at times, may be the only evidence of such dysfunction in patients with metastatic liver carcinoma and lymphoma. Cholinesterase levels may likewise be normal while other liver function tests are abnormal.

5. In general, normal serum cholinesterase activity is associated with a normal serum albumin level, but low enzyme activity does not necessarily indicate a low serum albumin level. In the great majority of patients with a low serum albumin level, the cholinesterase activity was also lowered.

6. Further investigation of the several factors influencing the serum cholinesterase activity, and in what manner and degree these factors operate, in warranted.

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RECURRENT PNEUMONIA IN MULTIPLE MYELOMA AND SOME OBSERVATIONS ON IMMUNOLOGIC RESPONSE *

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Over a period of several years, many patients with multiple myeloma and recurrent episodes of bacterial pneumonia have been observed at the University of Minnesota and the Minneapolis Veterans Administration Hospitals. However, the literature on multiple myeloma does not emphasize pulmonary infiltrates or recurrent pneumonia except as terminal events.[1-6] † For this reason it appeared desirable to gather evidence concerning bacterial pneumonia in myelomatosis and to investigate the immunologic response of patients with the disease.

Materials and Methods

The hospital records of 64 patients with multiple myeloma, observed at the University of Minnesota Hospitals from 1943 to 1953 and at the Minneapolis Veterans Hospital from 1946 to 1953, were reviewed. In all 64 cases the diagnosis of multiple myeloma was established by bone marrow biopsy or autopsy. Thirteen patients of the series had bacterial pneumonia, not including terminal bouts. Ten of the 13 patients had recurrent episodes.

In all 13 patients with pneumonia, the serum albumin-globulin ratio was measured according to Powers' modification of Kingsley's biuret method.[7] In five patients serum protein fractions were measured by Jager's modification of the Weichselbaum salt precipitation method.[8, 9] Electrophoretic determination of the serum protein fractions was done in four patients having pneumonia. The apparatus used was the portable model made by the American Instrument Company, operated at 10 ma. and allowing 120 minutes for separation. A veronal buffer was used at a pH of 8.55.

During the first nine months of 1953 we had the opportunity to study 10 consecutive cases of multiple myeloma, none of whom had had a pneumonic episode at the time of investigation. Their serum protein fractions, as established by electrophoresis, represented most of the usual myelomatous variations.[10-14]

These 10 patients were immunized by subcutaneous injection of 0.08 mg.

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† Recently recurrent pneumonia has been reported in 13 of 97 myelomatous patients by Snapper et al.[33]

each of pneumococcus polysaccharides, types I and II.* Seven of the patients were challenged later with 0.1 ml. of a 1:100 dilution of the polysaccharide fraction of *Brucella abortus* † and two weekly doses of 0.5 ml. typhoid-paratyphoid vaccine (Lederle). Normal adult controls were challenged with identical doses of the polysaccharides of pneumococcus, types I and II, and *Br. abortus*. Immunization of these controls with typhoid-paratyphoid vaccine was omitted because all had received this vaccine previously.

Precipitins for pneumococcus polysaccharides were tested by a modification of a method described by Kolmer and Boerner.[15] The undiluted serum was overlaid in glass capillary tubes with tenfold dilutions of the polysaccharide dissolved in 0.8 per cent NaCl solution, containing 0.01 M. Na_2HPO_4, adjusted to a pH of 7.2. The tubes were incubated at 37° C. for 30 minutes and then refrigerated at 4° C. for 12 hours before reading. The precipitate at the interface was graded 0, ±, +, ++, and +++. Quantitative measurements [16] of the pneumococcus polysaccharide precipitins in four controls showed a satisfactory agreement.

The determination of serum Brucella agglutinins was performed by the standard tube dilution method.[17] The agglutinins for *Salmonella typhosa* O and H antigens and *Salmonella paratyphi* A and B were determined by the rapid slide method.[18]

Results

The pertinent clinical data of 13 patients with bacterial pneumonia and multiple myeloma are presented in table 1. *Diplococcus pneumoniae* was cultured from the blood or sputum of seven patients on one or more occasions; there were three patients with pneumococcic bacteremia. The radiologic appearance of these pneumonias followed no uniform pattern. The variations ranged from early pulmonary congestion to lobar consolidation. Two episodes were associated with pleural effusion. The leukocytic response did not seem to deviate from the usual pattern. The clinical response to antibiotics was good, except for three cases with additional complications, such as advanced azotemia or coronary artery disease. There was only one case which exhibited poor resolution.

There was an unusual tendency towards recurrence of pneumonia, with 44 episodes in 10 patients. The pneumococcus was isolated from the sputum or blood during 12 pneumonic episodes in seven patients. Moreover, bacterial cultures of sputum or blood in three cases showed a pneumococcus, of the same type as originally isolated, as the cause of recurrences, in one case after an interval of more than two years. Patient C. L. had 13 bouts of pneumonia, four by history and nine observed during repeated hospitali-

* Generously supplied by Dr. Lawrence Hobson, Squibb & Co., 745 Fifth Ave., New York, N. Y.

† Provided by Dr. James Ruegsegger, Lederle Laboratories, Pearl River, N. Y.

TABLE 1

Data on 13 Patients with Multiple Myeloma and Pneumonia

Patient	Pneumonic Episodes	X-ray Findings*	Sputum† Culture	Blood† Culture	Blood Leukocytes		Treatment of Pneumonia‡	Result
					Total/mm.³	%Pmn.		
E. A. H.	2–16–44	LLL. Scatt. foci	Negative	D. pn. 4	10,000	72	Sulfadiazine & Penicillin	Good
	3–11–44	Path. fract. rt. humerus	Negative	D. pn. 4			Sulfadiazine & Penicillin	Good
C. W.	Fall '45	Not hosp.						
	8–20–52	Scatt. foci	Negative	—	11,000	76	Penicillin & OTC	Good
O. H.	Spring '47	Not hosp.					Sulfadiazine	Good
	Fall '47						Sulfadiazine	Good
	Fall '47						Sulfadiazine	Good
D. A. Y.	6– 6–47	LLL (consol.)	—	Negative	17,000	87	Penicillin	Good
	6– 1–48	RLL (congest.)	—	—	15,000	93	Penicillin	Good
	6–28–48	RUL (atelect.)	—	—	5,200	68	Penicillin	Good
E. F. G.	Jan. '49	"Left lung"					Penicillin	Good
	Feb. '49	"Left lung"					Penicillin	Good
	Mar. '49	"Left lung" Not hosp.					Penicillin	Good
	June '49	"Left lung"					Penicillin	Good
	2–28–50	RUL & RLL						Died
		Scatt. foci	D. pn. 3	Sterile	6,800	74	Penicillin	(BUN 130)
C. L.	(4 episodes in two years prior to first hosp.)							
	1–30–49	LLL & pl. eff.	Negative	D. pn. 18	16,600	87	Penicillin	Good
	3–11–49	LLL	α & β str.	Sterile	13,800	89	Penicillin	Good
	4–11–50	LLL (scatt. foci)	α strep.	Sterile	23,500	92	Penicillin	Good
	5– 1–51	LLL	D. pn. 22	D. pn. 18	18,500	86	Penicillin	Good
	5–15–51	LLL	D. pn. 22	Sterile	13,500	90	Penicillin	Good
	10–23–51	RLL & LLL	Negative	D. pn. 22	8,000	64	CTC	Good
	12–27–51	LLL	α strep.	D. pn.	19,700	85	Penicillin	Good
	5–12–52	RLL (consol.)	Proteus	Sterile	10,000	85	Pen. SM. DHSM. & OTC	Good
	6–11–52	RLL	Proteus	Sterile			Pen. SM. DHSM. & OTC	Died (BUN 42)

TABLE 1—*Continued*

Patient	Pneumonic Episodes	X-ray Findings*	Sputum† Culture	Blood† Culture	Blood Leukocytes		Treatment of Pneumonia‡	Result
					Total/mm.³	%Pmn.		
A. L. B.	March '49						Penicillin	Good
	Feb. '50	Not hosp.					Penicillin	Good
	March '50						Penicillin	Good
	3–31–50	Lt. hilum	D. pn. 5	Sterile	9,200	44	CTC	Good
H. P. D.	3– 6–50	RLL	Negative	—	8,800	70	CTC	Good
	4–16–50	LLL (consol.)	Negative	—			Penicillin	Good
	12–21–50	RLL & LLL (consol.)	D. pn. 19	—	14,200	84	CTC	Good
	1–16–52	Not hosp.					CTC	Good
F. A. B.	5– 1–50	LLL Not hosp.	Negative	—	6,300	75	Penicillin	Good
	10–10–50	RLL (consol.)	D. pn. 6	Sterile	17,200	91	Penicillin	Good
	1– 8–51	RLL (scatt. foci)	D. pn. 6	Sterile	11,100		Penicillin	Good
A. A. A.	7–28–51	RML & RLL (consol.)	D. pn. 13	D. pn. 13	6,700	80	Penicillin & CTC	Died (coronary sclerosis)
F. H.	9–10–51	LLL	α strep.	Staph. coag.	16,800	91	Penicillin	Good
			E. coli	+				
	10–13–52	Rt. lung (consol.)	*E. coli*	Sterile	11,500	82	DHSM & CTC	Poor resolution
J. G. W.	5–18–53	RLL (scatt. foci)	α strep.	Sterile	7,900	79	OTC	Good
M. E.	10– 1–53	LLL consol. & pl. eff.	Negative	Sterile	10,200	94	Penicillin & SM.	Good

* RUL—Right upper lobe
RML—Right middle lobe
RLL—Right lower lobe
LLL—Left lower lobe

† D. pn.—*Diplococcus pneumoniae*, type.
‡ Pen.—Penicillin
SM.—Streptomycin
DHSM.—Dihydrostreptomycin
OTC.—Oxytetracycline (Terramycin)
CTC.—Chlortetracycline (Aureomycin)

zations. In spite of successful penicillin therapy in January, 1949, *D. pneumoniae,* type 18, reappeared in his blood in May, 1951. *D. pneumoniae,* type 22, was encountered in this man's sputum in May, 1951, and in his blood culture five months later. The course of this patient and of two others suggested that the pneumococci were not eliminated by penicillin in doses which are adequate in patients without myeloma.

Patient E. A. H. suffered a pathologic fracture of the right humerus one month after pneumonia due to *D. pneumoniae,* type 4. Bacteremia recurred with the same organism and suggested the possibility of survival of some of the bacteria in the myelomatous tissue. This occurred in spite of treatment with sulfadiazine and penicillin. *D. pneumoniae,* type 6, was recov-

TABLE 2

Serum Proteins in 13 Patients with Multiple Myeloma Complicated by Pneumonia

Patient	Albumin	Globulin					Total Serum Proteins
		Total	Alpha	Beta	"M"	Gamma	
E. A. H.	2.2	3.8					6.0
C. W.†	2.1	7.7	0.6	0.5		6.6	9.8
O. H.	3.1	6.7					9.8
D. A. Y.	3.4	11.2					14.6
E. F. G.†	2.3	7.3	1.6	1.6		4.1	9.6
C. L.*	0.8	11.3	1.7	7.4		2.2	12.1
A. L. R.*	2.7	9.1	0.8	1.3		7.0	11.8
H. P. D.*	2.9	4.8	1.2	0.6		3.0	7.7
F. A. B.*	2.7	4.1	1.5	0.4		2.2	6.8
A. A. A.	3.6	9.4					13.0
F. H.*	2.5	5.3	1.5	1.4		2.4	7.8
J. G. W.†	3.6	2.6	1.3	0.6		0.7	6.2
M. E.†	2.0	4.8	1.0	0.5	2.5	0.8	6.8

* By chemical fractionation, in gm./100 ml.
† By electrophoretic fractionation, in gm./100 ml.

TABLE 3

Serum Proteins in 10 Patients with Multiple Myeloma and No Pneumonia

Patient	Albumin*	Globulin*					Total Serum Proteins*
		Total	Alpha[1]	Alpha[2]	Beta	Gamma	
C. W.	3.5	6.3	0.3	0.5	0.4	5.1	9.8
A. J.	3.5	5.2	0.4	0.9	1.0	2.9	8.7
C. H.	2.8	6.3	0.4	0.5	0.6	4.8	9.1
F. T.	2.9	9.9	0.4	1.1	1.0	7.4	12.8
H. S.	2.8	5.1	0.3	0.8	3.5	0.5	7.9
E. S.	4.1	3.6	0.5	0.9	1.6	0.6	7.7
E. C.	2.8	3.3	0.4	0.9	1.0	1.0	6.1
H. M.	4.2	2.9	0.3	0.6	1.0	1.0	7.1
J. G. W.	3.6	2.6	0.6	0.6	0.6	0.7	6.2
E. J.	3.3	2.2	0.5	0.5	0.6	0.6	5.5
Mean	3.4	4.7	0.4	0.7	1.1	2.5	8.1

* In gm./100 ml., by electrophoresis.

ered from the sputum of patient F. A. B. during recurrent pneumonia three months after a pneumonia due to the same type of pneumococcus.

Table 2 shows the serum protein values in these 13 patients. Only the albumin-globulin ratio had been determined in four patients. The serum of five was more completely fractionated by chemical methods, whereas the remaining four were evaluated electrophoretically. It has been established that chemical fractionation yields lower values for gamma globulins than are obtained by electrophoresis.[9] However, the nine sera which were more completely fractionated represent the gamut of the established myeloma

TABLE 4

Precipitin Tests in Sera of 10 Patients with Multiple Myeloma Before and After Immunization with 0.08 mg. of Pneumococcus Polysaccharides, Types I and II

	Prior to Immunization						Three Weeks after Immunization				
	Dilution	1:500	1:5,000	1:50,000	1:500,000	1:5,000,000	1:500	1:5,000	1:50,000	1:500,000	1:5,000,000
Patient	Pn. Polysacch. type										
C. W.	I	0*	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
A. J.	I	0	0	0	0	0	+	0	0	0	0
	II	0	0	0	0	0	±	0	0	0	0
C. H.	I	0	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
F. T.	I	0	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
H. S.	I	0	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
E. S.	I	0	0	0	0	0	+	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
E. C.	I	0	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
H. M.	I	0	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
J. G. W.	I	0	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0
E. J.	I	0	0	0	0	0	0	0	0	0	0
	II	0	0	0	0	0	0	0	0	0	0

* Recording scale of precipitate (0, ±, +, ++ and +++).

patterns. In this small group there was no convincing relation between the serum protein pattern and the frequency or severity of the pneumonic episodes.

The serum protein values of 10 cases of myelomatosis without pneumonia were determined by electrophoresis and are presented in table 3. There were four sera with the typical gamma pattern, two showed the beta pattern, and two presented borderline values for their beta and gamma components, whereas the remaining two were essentially normal. No "M" pattern was contained in this group. With this one exception the group was typical of the variations of abnormal globulins found in multiple myeloma.[10-14] On

the whole, the patterns did not differ greatly from those in the 13 patients with pneumonia. However, there was a larger proportion of nearly normal patterns in the patients who did not have pneumonia.

Table 4 shows the very feeble or absent precipitin response in 10 patients with multiple myeloma after subcutaneous immunization with 0.08 ml. each of pneumococcus polysaccharides, types I and II. This has been compared to the much greater response of 10 normal adult controls to the identical challenge (table 5).

TABLE 5

Precipitin Tests in Sera of 10 Normal Adult Subjects Before and After Immunization with 0.08 mg. of Pneumococcus Polysaccharides, Types I and II

		Prior to Immunization					Three Weeks After Immunization				
	Dilution	1:500	1:5,000	1:50,000	1:500,000	1:5,000,000	1:500	1:5,000	1:50,000	1:500,000	1:5,000,000
Control	Pn. Polysacch. type										
H. Z.	I	0*	0	0	0	0	+++	+++	++	++	++
	II	0	0	0	0	0	+++	+++	++	++	++
E. B.	I	0	0	0	0	0	++	++	+	±	+
	II	0	0	0	0	0	++	+	+	+	+
G. H.	I	0	0	0	0	0	++	++	++	++	+
	II	0	0	0	0	0	++	++	++	++	++
H. K.	I	0	0	0	0	0	++	++	++	++	++
	II	0	0	0	0	0	++	++	++	++	±
H. B.	I	±	0	0	0	0	++	++	++	++	++
	II	0	0	0	0	0	+	++	++	++	++
R. S.	I	0	0	0	0	0	++	++	++	++	++
	II	0	0	0	0	0	+	±	+	+	+
T. S.	I	0	0	0	0	0	0	±	+	+	+
	II	+	±	±	±	±	±	±	+	±	±
F. M.	I	0	0	0	0	0	+	+	+	+	+
	II	0	0	0	0	0	++	++	+	+	+
C. B.	I	0	0	0	0	0	+	+	++	+	0
	II	0	0	0	0	0	++	+	+	0	0
S. L.	I	+	0	0	0	0	++	+	±	0	0
	II	0	0	0	0	0	±	+	±	±	±

* Recording scale of the precipitate (0, ±, +, ++ and +++).

Seven of the 10 patients with myeloma were also challenged by the subcutaneous administration of 0.10 ml. of a 1:100 dilution of the polysaccharide fraction of *Br. abortus* (table 6). With one exception (patient J. G. W.), specific agglutinins failed to develop. Blocking tests were carried out with the post-immunization serum of one patient and proved negative. All seven normal controls responded with agglutinins in titers of 1:80 to 1:320. The only patient (J. G. W.) with myeloma who developed an adequate Brucella agglutinin titer had normal serum protein values (table 3).

Table 7 shows the response of the same seven patients with myeloma to typhoid-paratyphoid vaccine. The overall response was very weak. Three patients failed to develop agglutinins to any of the antigens. Patient J. G. W. again showed a good response, and patient E. J., the only other

patient with normal serum proteins, developed agglutinins for *S. paratyphi* A in a dilution of 1:40. Patients E. C. and H. M. developed weak agglutinins in dilutions to 1:40 and had "borderline" serum protein patterns, as can be seen in table 3. The three patients who failed to develop agglutinins had definitely abnormal serum globulins (table 3).

TABLE 6

Agglutinins in Sera of Seven Patients with Multiple Myeloma and Seven Normal Adults Before and After Immunization with 0.10 ml. of a 1:100 Dilution of Polysaccharide Fraction of *Brucella abortus*

	Prior to Immunization						Three Weeks After Immunization					
Dilution...	1:20	1:40	1:80	1:160	1:320	1:640	1:20	1:40	1:80	1:160	1:320	1:640
Patients												
A. J.	0*	0	0	0	0	0	0	0	0	0	0	0
C. H.	0	0	0	0	0	0	0	0	0	0	0	0
F. T.	0	0	0	0	0	0	0	0	0	0	0	0
E. C.	0	0	0	0	0	0	0	0	0	0	0	0
H. M.	0	0	0	0	0	0	0	0	0	0	0	0
J. G. W.	0	0	0	0	0	0	+	+	+	+	0	0
E. J.	0	0	0	0	0	0	0	0	0	0	0	0
Controls												
H. Z.	0	0	0	0	0	0	+	+	+	+	+	0
H. B.	0	0	0	0	0	0	+	+	+	±	0	0
R. S.	0	0	0	0	0	0	+	+	+	0	0	0
T. S.	0	0	0	0	0	0	+	+	+	±	0	0
F. M.	0	0	0	0	0	0	+	+	+	+	0	0
C. B.	0	0	0	0	0	0	+	+	0	0	0	0
S. L.	0	0	0	0	0	0	+	+	+	0	0	0

* Recording scale of agglutinins (complete agglutination +, incomplete agglutination ±, and no agglutination 0).

COMMENT

Humoral and cellular immune factors are the two major natural defense lines against pneumococcic invasion of the animal organism. Clinical resistance to pneumonia can be correlated with the appearance of antibodies to type-specific polysaccharides, and their absence is linked with a diminished clinical resistance to this infection.[20, 21] Indeed, in the period preceding modern chemotherapy, type-specific immune serum constituted our most potent therapeutic weapon against pneumococcus pneumonia.

Immune sera are not bactericidal against pneumococci per se, but exert their activity only in the presence of phagocytes. These cells have been shown to develop active phagocytosis without the aid of immune bodies, but their phagocytic activity is enhanced by antibodies.[20, 22] The plasma cell probably is the site of production of humoral antibodies.[23] However, the plasma cells in multiple myeloma are immature. Perhaps they do not form antibodies in the normal manner.

The pneumonia of our patients responded promptly to conventional antibiotic therapy, yet we observed recurrences of pneumonia caused by the same organism. One might be tempted to assume that there was in these patients

TABLE 7

Agglutinin Titers in Sera of Seven Patients with Multiple Myeloma Before and After Immunization with Two Weekly Doses of 0.5 ml. of Typhoid-Paratyphoid Vaccine

		Prior to Immunization						Three Weeks after Immunization					
	Dilution	1:20	1:40	1:80	1:160	1:320	1:640	1:20	1:40	1:80	1:160	1:320	1:640
Patient	Antigen												
A. J.	Ty. H.	0	0	0	0	0	0	0	0	0	0	0	0
	Ty. O.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. A.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. B.	0	0	0	0	0	0	0	0	0	0	0	0
C. H.	Ty. H.	0	0	0	0	0	0	0	0	0	0	0	0
	Ty. O.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. A.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. B.	0	0	0	0	0	0	0	0	0	0	0	0
F. T.	Ty. H.	0	0	0	0	0	0	0	0	0	0	0	0
	Ty. O.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. A.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. B.	0	0	0	0	0	0	0	0	0	0	0	0
E. C.	Ty. H.	0	0	0	0	0	0	0	0	0	0	0	0
	Ty. O.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. A.	0	0	0	0	0	0	+	0	0	0	0	0
	Para. B.	0	0	0	0	0	0	0	0	0	0	0	0
H. M.	Ty. H.	0	0	0	0	0	0	+	0	0	0	0	0
	Ty. O.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. A.	0	0	0	0	0	0	+	+	0	0	0	0
	Para. B.	0	0	0	0	0	0	+	+	0	0	0	0
J. G. W.	Ty. H.	0	0	0	0	0	0	+	+	+	+	0	0
	Ty. O.	0	0	0	0	0	0	+	+	+	+	0	0
	Para. A.	0	0	0	0	0	0	+	+	+	+	+	0
	Para. B.	0	0	0	0	0	0	+	+	+	+	0	0
E. J.	Ty. H.	0	0	0	0	0	0	0	0	0	0	0	0
	Ty. O.	0	0	0	0	0	0	0	0	0	0	0	0
	Para. A.	0	0	0	0	0	0	+	0	0	0	0	0
	Para. B.	0	0	0	0	0	0	+	+	0	0	0	0

a decrease of humoral antibody response similar to the type-specific "immunologic paralysis" produced experimentally by Felton.[24] Our experimental evidence shows a decrease in immunologic response, not only to pneumococci but also to several other bacterial antigens as well. None of the antigens was administered in doses "immunologically paralyzing" for normal adults.

Among our 13 patients with multiple myeloma and pneumonia we found an unusual tendency towards recurrence of the infection. *D. pneumoniae* was cultured from the sputum or blood of seven patients. In three cases the recurrent pneumonias were due to the original bacterial agent. One patient (C. L.) had 13 bouts of pneumonia. In spite of penicillin in January, 1949, *D. pneumoniae*, type 18, reappeared in this man's blood culture more than two years after its original appearance. *D. pneumoniae*, type 22, which was encountered in his sputum during two separate pneumonic

episodes in May, 1951, appeared in his blood five months later, though penicillin and chlortetracycline had been given. These observations suggest that the failure to develop humoral antibodies may prevent the complete elimination of pneumococci in spite of penicillin and other antibiotics.

The radiologic appearance of pneumonia in our myelomatous patients varied from minimal infiltrates to lobar consolidation. Only two of the latter were associated with pleural effusion. The leukocytic response during pneumonia was not deficient. The immediate clinical response of the pneumonia to antibiotics appeared to be prompt and satisfactory.

These 13 patients failed to demonstrate a clear relationship between serum protein abnormality and the frequency or severity of their recurrent pneumonias. However, all patients with markedly abnormal protein patterns had recurrent bouts, and one patient with a normal protein pattern has had but one episode.

Correlation of experimental humoral immune body response to typhoid, paratyphoid and Brucella antigens with the serum globulin pattern in seven myeloma patients without pneumonia suggested a definite relationship (tables 3, 6, 7). Larson and Tomlinson [25] studied 12 patients with low serum albumin and abnormally high gamma globulin. These patients included four with hepatic cirrhosis, four with multiple myeloma, and one each with Hodgkin's disease, bronchiectasis, disseminated lupus erythematosus and diabetes mellitus. After injection of type-specific pneumococcus polysaccharides the four patients with multiple myeloma showed poor antibody response.* It was suggested that their antibody formation became weaker with increasing amounts of serum gamma globulin. Their eight patients with increased serum gamma globulin, not caused by myeloma, presented normal or enhanced antibody response. The antibody production of our myeloma patients upon the challenge with pneumococcus and brucella polysaccharides and typhoid-paratyphoid antigens was uniformly poor. In accord with the previous impressions, the development of antibodies in multiple myeloma occurred in inverse ratio to the amount of serum globulins.

In multiple myeloma the increased serum globulins appear to be different from those found in normals or in most other diseases by chemical, physical and immunochemical standards.[19] This is suggested by the discrepancies in the comparison of electrophoretic and chemical protein determinations. Also, Kunkel and his group [27] demonstrated by immunochemical absorption methods that the gamma globulin of myeloma sera often is not completely absorbed by normal anti-gamma globulin rabbit serum, and that some myeloma globulins produce specific antisera in rabbits which fail to react with normal human serum components.

Immunochemical abnormalities of the serum globulins of our 10 myeloma patients may well have been responsible for the extremely poor antibody response to experimental antigenic challenges. Indeed, the response to

* Layani et al. found a diminished antibody response to tetanus toxoid in one patient with multiple myeloma and another with hyperglobulinemia and plasmacytosis.[26]

Brucella and typhoid-paratyphoid antigens suggests that we may expect in myeloma an increasingly poor antibody response with increasing elevation of the serum globulin levels. Waldenström suggested that the pathologic globulin fractions may have a higher priority for the available amino acids than albumin or the normal antibodies.[13]

Our experience with recurrent episodes of pneumococcus pneumonia in three cases of agammaglobulinemia [28] and previous reports of similar patients from other sources [29–32] are particularly interesting in regard to these myelomatous patients. Patients with multiple myeloma, as well as those with agammaglobinemia, have characteristic abnormalities of their gamma globulins. Although the gamma globulins of these two conditions are diametric opposites by quantitative measurement, with an abnormal excess in one and near-absence in the other, they have in common a profound reduction of their immunologically active serum globulins. In both conditions bacterial infections tend to be recurrent, although they show a good immediate response to antibiotic therapy.

Summary and Conclusions

Review of the clinical records of 64 patients with multiple myeloma showed a marked tendency to recurrent bouts of bacterial pneumonia. The immediate response of these infections to antibiotics was good.

Ten myelomatous patients without pneumonia were subjected to challenges with the polysaccharides of pneumococci and *Br. abortus* and with typhoid-paratyphoid vaccine. The serum antibody response was poor. There was evidence to suggest that the antibody production occurred in inverse ratio to the amount of abnormal serum globulins.

Poor antibody response and recurrent pneumonia in multiple myeloma and agammaglobulinemia make these two quite different diseases appear immunologically similar. In both, recurrent pneumonia is the result of a poor antibody response.

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SIMPLICITY IN THE TREATMENT OF MENINGITIS *

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MANY of the early methods for the treatment of meningitis have been forgotten or largely abandoned. Nevertheless, there are well qualified physicians who continue to espouse original procedures which are unnecessary for the benefit of patients. To appreciate fully the advances [1] that have taken place it seems almost imperative to cite some of the history of the therapy of meningitis.

Kolle and Wasserman [2] in 1906 were the first to report a specific remedy for any kind of meningitis, based on animal experimentation. This was an antibacterial serum for meningococcic infections, which Jochmann [3] developed still further in the same year for clinical intrathecal use. In 1907 Flexner [4] announced his improved serum, which was polyvalent, and it was first used in that year during an epidemic in Akron, Ohio.

From the beginning it was felt that anti-meningococcus serum must be brought into direct contact with the organisms in the cerebrospinal fluid. Consequently, the routine method of administration throughout the world was by means of lumbar puncture. During World War I Herrick [5] advised intravenous serum for patients with meningococcemia. This latter procedure, however, still conformed to the existing view that the remedy must be in direct contact with the offending organisms to be effective, a theory which many are still reluctant to discard.

It was reported that the Flexner serum brought about a reduction of approximately 35 per cent in the fatality rate for meningococcic meningitis. This was a great accomplishment, because practically all other bacterial infections involving the meninges were almost uniformly fatal. However, there were still far too many deaths [8] from meningococcic infections, and also many serious complications among those who survived. In contagious disease hospitals where large numbers of patients were admitted, survival rates above 50 per cent were considered exceptionally good. Some of the states reported fatalities as high as 69 per cent, and even as late as 1930, which was 23 years after the introduction of serum, the Ministry of Health [9] announced a death rate of 95.1 per cent for meningococcic meningitis in England and Wales.

There was dissatisfaction with the commercial polyvalent serum, and various means were devised to improve recovery rates and diminish complications.[10] Typing of meningococci from the spinal fluid was a common requirement to determine if a particular product should be effective. Oc-

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From the Cook County Contagious Disease Hospital.

casionally monovalent serums were prepared for the type of meningococcus that prevailed.

In some cities antiserum was administered intraspinally as often as two to three times in 24 hours during the first few days and finally but once daily. Patients were commonly in a state of opisthotonos during a portion of their illness. Blocks often occurred in the spinal canal, and then serum was given intracisternally, or sometimes oxygen was introduced in the lumbar region for the purpose of relieving the obstruction. In young infants serum frequently was injected into the lateral ventricles. Few patients under one year of age recovered, however, and those who survived generally had hydrocephalus or perhaps loss of sight or hearing. The fate of those beyond 35 was not much better, for the death rate rose rapidly with advancing years.

Fever therapy was suggested as an effective method of treatment, and a few favorable reports were published, but the fever cabinet as a substitute for serum was never adopted on an extensive scale. Another form of treatment seems interesting to recall, even though it was never used extensively. Kersch, of Rock Island, Illinois, advocated chemotherapy and manufactured for the purpose preparations supplied in ampules for intravenous injection. Among the ingredients in the remedy were iodides and guaiacol, if I recall correctly. Kersch traveled about the country conducting postgraduate courses for physicians and expounding the purposes and value of chemotherapy for a variety of infections. This was approximately 10 years before the introduction of the sulfonamides and chemotherapy as we know it today. Although a number of reports from physicians in scattered areas endorsed the chemotherapeutic solutions, the theory seemed too drastic for general acceptance and was almost totally ignored.

Another factor of extreme concern, and one which some continue to view with too great alarm, was the danger of increased intracranial pressure.[11] To offset such a possibility, frequent lumbar punctures were required for drainage, and special needles were devised which could be left in place for indefinite periods for continuous drainage of cerebrospinal fluid. To facilitate that aim, the patient was sometimes placed on a Bradford frame.

In 1933, following animal experimentation, Ferry produced his meningococcus antitoxin, which was first used at the close of that year for the treatment of patients in Cook County Contagious Disease Hospital.[11] Like the antibacterial preparations, it was a horse serum. It was presumed to be effective against all four Gordon-Murray types of meningococci. In the beginning it was administered both intraspinally and intravenously. By the latter route it was given in large doses well diluted in 10 per cent glucose. Before long, however, the intrathecal route was abandoned for most patients at County Hospital. Opisthotonos then was seldom observed, and fatality rates declined sharply. Also, complications were far fewer, and recovery was frequently complete in 10 days or two weeks. This period of treat-

ment contrasted with four to five weeks or more when serum was used intrathecally.

Reference has been made to the presence of opisthotonos when there was intraspinal therapy. Other complications involved the eyes and ears. In one series of cases 6 per cent had an endophthalmitis or panophthalmitis which resulted in loss of sight in one or both eyes. Complete loss of hearing was not rare and arthritis was common, although suppuration of the joints seldom occurred. Meningococci often persisted in the cerebrospinal fluid for several weeks, and isolation of patients was required until negative cultures had been obtained.

Relapses were not unusual during the course of intraspinal treatment, and from time to time recurrences were witnessed several weeks after the patient had left the hospital apparently cured. Such happenings as these are seldom encountered now and were attributed to adhesions in the spinal canal which harbored the organisms. Even after patients had recovered from meningitis it was sometimes necessary for them to consult an orthopedist.[13] This was because, as a result of numerous lumbar punctures, there had been injuries to intervertebral discs and relief was sought for painful backs.

There were three objectives in making frequent lumbar punctures: (1) to introduce an antiserum, (2) to relieve intracranial pressure, and (3) for laboratory examination of cerebrospinal fluid.

It has long been my contention that intrathecal treatment is not necessary [14] and therefore should be regarded as contraindicated [15] for any kind of meningitis. No permanent benefit is derived by frequent withdrawal of spinal fluid for the purpose of relieving intracranial pressure, nor ought there be a demand for lumbar punctures daily or every other day in order to have the laboratory make a report on the patient's progress.

The primary purpose for a lumbar puncture should be for diagnosis.[16] More than one puncture is seldom required for purulent meningitis. In tuberculous meningitis there may be difficulty in detecting the organism and more than one puncture is often justified. If a meningitis patient has petechiae in the skin and a smear from one of the lesions discloses the gram-negative organism, no spinal taps are needed.[17] The same holds true if a positive blood culture has been obtained for the offending organism.

After an etiologic diagnosis of meningitis has been determined it is merely necessary now to select one of a number of drugs which have been proved to be effective against the organism concerned. If response to the remedy does not seem to be satisfactory, then sensitivity tests with other drugs should be made.

One may inquire, What about spinal fluid levels [18] for the prescribed drug? This is one of the questions commonly asked, but it is not so important as one might believe. The concentration of the remedy in the lumbar region is not necessarily the same as it is about the brain. How-

ever, it has been estimated that the spinal fluid level averages from 50 to 75 per cent of the blood level.

Medication may be administered intravenously, orally or, if necessary, intramuscularly.[19] Recovery is possible by any one or by a combination of these methods. Therefore, there is no necessity of possessing special skill in performing lumbar punctures. If an appropriate drug is available for the purpose the intravenous route for the initial dose of the remedy seems best for a prompt response to treatment.

With scientific facts firmly established there is no need to resort to laboratory investigations merely to test their accuracy. Frequent examinations of the spinal fluid as a guide to the patient's progress are entirely unnecessary. It is known that if the reaction to treatment is favorable a high cell count will diminish and a low content of glucose will rise. When the patient is clinically well one has a right to assume that the spinal fluid is approximately normal. We should not assume, however, that every patient ought to be entirely well after three to four days of treatment. A temperature above normal does not always justify a puncture to determine if there is a subdural effusion. However, exclusive of tuberculous infections, the majority of our patients have recovered in from 10 to 12 days, some in shorter periods.

TABLE 1

1953

Cook County Contagious Disease Hospital

MENINGITIS

MENINGOCOCCIC

Under 1 Year	1–5	6–15	16–45	Over 45	Total	Deaths	Fatality %
13	33	15	11	7	79	8	10

PNEUMOCOCCIC

There were 16 patients with 9 deaths (mostly over 45)

HEMOPHILUS INFLUENZAE

1	3	1	1	6	1	16

TUBERCULOUS

	4	5	2	11	5	45

Several thousand patients with various forms of meningitis have been given successful treatment based on the convictions expressed in this paper. During the past year at Cook County Contagious Hospital there were 79 patients with meningococcic infections, with eight deaths, or a fatality rate of 10 per cent. Four of the patients who succumbed had a Waterhouse-Friderichsen syndrome. One of the remaining deaths occurred in the receiving room before examination was complete. During 1953 there were also 16 patients with pneumococcic meningitis, and nine of these terminated fatally. Most of the deaths occurred in those who were beyond 45 years

of age, whose general condition was poor. Among six patients with *Hemophilus influenzae* meningitis there was one death. A particularly interesting case was included in this latter group. A woman, 55 years of age, was admitted in coma with stiffness of the neck. An accompanying history disclosed that she had diabetes. A purulent fluid was released by lumbar puncture. It was thought that the patient probably had a pneumococcic meningitis. Before the laboratory report on the spinal fluid was received Acromycin was administered intravenously. Within three days the patient's temperature declined to normal and she was fully rational. Then a laboratory report was received showing positive culture for *H. influenzae* from the spinal fluid. Since about 90 per cent of influenzal meningitis cases occur before five years of age, it is quite unusual to see this type of infection in one of such years. Her speedy and complete recovery was dramatic.

The treatment of tuberculous meningitis among our hospital admissions has been regarded as fairly satisfactory considering the nature of the disease. The general management of these patients has been much the same as for other kinds of meningitis, except that the period of medication must continue for many months.

During the past year there were five deaths from tuberculous meningitis, but six patients were released from the hospital to their homes. Two of the six appeared to be in excellent health and during a period of several months have gained considerable weight and seem to be well. Among the others, a woman of 35 years was in fair condition, and the same statement applies to a man. Two children, however, one 18 months and the other three years of age, had by no means overcome a disease which threatened their existence. None of the patients with tuberculous meningitis received any intrathecal treatment, and without that procedure their late care at home is simplified. Isoniazid orally can be used.

In conclusion, it may be said that important assets in the successful treatment of meningitis are sense and simplicity in the mode of management.

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ACUTE INTERMITTENT PORPHYRIA: A REPORT OF FIVE CASES AND A REVIEW OF THE LITERATURE*

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INTRODUCTION

SINCE the review of porphyria by Mason, Courville, and Ziskind [1] 20 years ago, and Waldenstrom's classic description of the acute disease in 1937,[3] there have been a number of advances in the biochemistry of the porphyrins, stemming in great part from the laboratory of Watson and his associates.[2, 65, 66] In 1941 these investigators described a simple test (Watson-Schwartz test) for the demonstration of porphobilinogen in the urine which has greatly facilitated the diagnosis of acute intermittent porphyria [4] and which has gained wide acceptance.[59]

The following is a report of five patients with acute intermittent porphyria studied in the past nine years (four in the past two and one-half years). All five patients had been under prolonged medical care without an accurate diagnosis, and each had had at least one laparotomy. A review of the case reports in the English language, from 1941 to March, 1953, has been made in an attempt to define the type of patients who should be screened for acute intermittent porphyria by means of the Watson-Schwartz test.

METHOD

The cases reported in the literature were accepted as being acute intermittent porphyria if they fulfilled the following criteria:

1. The presence of porphobilinogen or uroporphyrin or both in the urine. The statement that "porphyrins were found in the urine" was considered insufficient evidence.
2. All patients with photosensitivity were excluded.
3. Only symptomatic patients were included, thereby excluding those with "latent" porphyria.

In some instances, adhering to these criteria resulted in the inclusion of patients reported as chronic porphyria or hematoporphyrinuria. On the other hand, all cases of "porphyria without porphyrinuria" [50] were excluded because the diagnosis remains in doubt.

Including the five patients reported here, there were 69 case reports [7-16, 18-27, 29-31, 33-40, 42-58] which satisfied the above criteria.

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Nomenclature and Classification

Porphyrinuria denotes any condition in which an excess of coproporphyrin or uroporphyrin or both is found in the urine. This includes not only the disease porphyria but also many other conditions in which abnormal amounts of coproporphyrin are excreted in the urine.

The disease porphyria is thought to be a constitutional defect leading to a disturbance in the metabolism of pyrroles, which in turn results in the excretion of abnormal types and amounts of porphyrins in the urine. Many classifications of the disease have been made, the most common being:

1. Congenital (photosensitive)
2. Acute, intermittent
3. Chronic (cutanea tarda) (mixed)

However, the acute type can become chronic and is possibly inherited, the chronic type also may exhibit photosensitivity, and the symptoms of the congenital type may not be present at birth. Watson and his co-workers,[2] therefore, proposed a new classification, based on their concept of the site of origin of the porphyrin of abnormal quantity and type found in the urine of these patients:

1. Porphyria erythropoietica, indicating that porphyrins are found in large amounts in the bone marrow. There are red staining of the teeth and bones, photosensitivity and splenomegaly. This corresponds to the congenital type in the old classification.
2. Porphyria hepatica, which suggests the liver as the site of formation of abnormal types and increased amounts of porphyrins. Porphyria hepatica is further subdivided into two subtypes:

a. Acute intermittent porphyria, the most common porphyria.
b. Mixed porphyria,[61] which is distinguished from the acute type mainly on the basis of photosensitivity.

Case Reports

Case 1. A 40 year old housewife entered the hospital complaining of pain and weakness in her arms and legs of two months' duration.

The patient had been well until July, 1949, when severe abdominal pain developed and recurred at intervals for a year. During an acute episode of pain an appendectomy, a hysterectomy and a unilateral oophorectomy were performed. Postoperatively, the pain persisted for two months.

In November, 1950, four months postoperatively, severe abdominal pain recurred and the patient was studied at another institution. The blood pressure was 120/80 mm. of Hg, and the neurologic examination was normal. A flat plate of the abdomen was suggestive of obstruction of the small bowel but a barium enema on the following day was normal. The leukocyte count was 11,100 per cubic millimeter, and the erythrocyte sedimentation rate was 36 mm. per hour.

The patient was referred to a psychiatrist, who believed she was a "person of

poorly integrated and immature personality, finding a secondary gain in prolonging her illness." The impression was psychoneurosis, conversion hysteria. The patient slowly improved and could stand with help by December, 1950.

In February, 1951, pain recurred in the shoulders, arms and hands. The blood pressure was 130/80 mm. of Hg; pulse, 84; temperature, 98.2° F. The liver was palpable three fingerbreadths below the right costal margin. The deep tendon reflexes were absent in the upper extremities and diminished in the lower. There was no sensory deficit. Shortly thereafter we saw her for the first time.

Physical Examination on Admission: The patient was a thin woman with a high-pitched, whining voice who was very irritable and cried easily. The blood pressure was 150/110 mm. of Hg and the pulse rate 92 per minute.

There were slight muscular imbalance in the extraocular movements and poor approximation of the vocal cords. Wasting of the muscles of the extremities was marked. There was mild edema. A symmetric flaccid paralysis of the hands was noted. The feet, legs and arms were markedly weak. The deep tendon reflexes were absent initially, but later the quadriceps reflexes were absent while the achilles reflexes were present. Sensation was intact, but the skin and muscles were very tender on palpation.

The remainder of the examination was noncontributory.

Laboratory Findings: The urine was a light amber color, and urinalysis was negative except for a positive Watson-Schwartz test. Uroporphyrin and an increased amount of coproporphyrin were also demonstrated in the urine. The leukocytes numbered 5,580 per cubic millimeter, and the nonprotein nitrogen ranged between 35 and 44 mg. per cent. Liver function tests, serum electrolytes and the fasting blood glucose level were all normal.

Lumbar puncture revealed a 3 plus Pandy's test, but the protein was only slightly elevated at 72 mg. per cent. There were 5 mononuclear cells per cubic millimeter, and culture was negative. The electrocardiogram showed sagging ST in I, II, III, AVF and V5, which was interpreted as evidence of myocardial anoxia.

A muscle biopsy showed encysted trichinae and moderate atrophy of muscle. After a test dose of 25 mg. of ACTH intravenously, the eosinophil count dropped 73 per cent in four hours.

In the radial and femoral nerves there was no response to faradic stimuli and only a poor response in the median, ulnar and peroneal nerves.

Course of the Disease: The patient was very irritable and uncoöperative throughout her hospital stay. Improvement was gradual, but marked. Therapy consisted of 2 gm. of potassium chloride and 10 mg. of riboflavin four times daily. One gram of glycine was also given daily, in divided doses. Enemas were needed frequently because of severe constipation. After a month, the patient left the hospital against medical advice.

Two years later the patient's right leg and foot dragged slightly when she walked, but there had been no further episodes of pain. She did all of her own housework and seemed quite cheerful. The Watson-Schwartz test was still strongly positive.

Comment: This patient demonstrates the triad of abdominal pain, peripheral neuropathy and psychic change typical of acute intermittent porphyria. The diagnosis was confirmed by a strongly positive Watson-Schwartz test for porphobilinogen. Two years later, despite her almost complete recovery, the test remained strongly positive. The trichinae in the muscle biopsy are considered to be an incidental finding, as no other mention of the coexistence of porphyria and trichinosis has been found.

Case 2. A 36 year old former nurse and doctor's wife was admitted on April 29, 1952, with the complaints of generalized muscle pain, weakness and a stiff right fifth finger for eight months, and low back pain for 15 years.

At the age of eight the patient had had frequent episodes of "burning muscles," and at 19 an appendectomy was performed for a "ruptured appendix." Two years later an ovarian cyst was removed, and since then she has also complained of low back pain. From 1938 to 1949, frequent mild abdominal cramping was ascribed to a "spastic colon."

Three years prior to admission (age 34) a hysterectomy was done for "endometriosis." Two months after this operation the patient became weak, and a diagnosis of Guillain-Barré syndrome or alcoholic polyneuritis was made in another institution. At that time the cerebrospinal fluid protein was 70 mg. per cent. Although mild weakness of the right leg persisted, the patient was able to resume her activities after three months.

Beginning in 1949 the patient had frequent muscle cramps in the right arm on exertion, and in August, 1951, the fifth finger of the right hand became swollen and painful, and a diagnosis of rheumatoid arthritis was made. A two-week course of cortisone, 25 mg. four times a day, did not relieve the pain. Two months before admission the patient became bedfast because of weakness and the burning pain in her muscles. In another hospital the diagnoses of "rheumatoid arthritis, acute polyneuritis, and myopathy of the right leg" were made. A muscle biopsy was normal, as were x-rays of the chest, long bones and joints. The sedimentation rate, erythrocyte and leukocyte counts, and nonprotein nitrogen were also normal. The cerebrospinal fluid contained four lymphocytes and 63 mg. per cent protein. Sternal marrow aspiration revealed a moderate increase in eosinophils. We first saw the patient shortly thereafter.

Physical Examination on Admission: The patient was sobbing and complaining of pain. She was very irritable and uncooperative, and at other times quite belligerent and aggressive. The blood pressure was 160/82 mm. of Hg; pulse, 80 per minute; the temperature was normal. On the forehead there were areas of hypo- and hyperpigmentation, and there was a small spot of brown pigment on the buccal mucosa. The fifth finger of the right hand was tender and slightly swollen, and the muscles generally were tender.

The cranial nerves were intact, and the deep tendon reflexes were normal. There was questionable weakness of the right leg. The remainder of the examination was noncontributory.

Laboratory Findings: The Watson-Schwartz test was positive. Uroporphyrin and an increased amount of coproporphyrin were demonstrated in the urine. On one occasion a nine and one-half hour specimen of 450 c.c. of urine contained 49.58 μg. of uroporphyrin. The hemoglobin, hematocrit, white cell count, nonprotein nitrogen, fasting blood glucose and serum electrolytes were all normal. The erythrocyte sedimentation rate was 42 mm. per hour. 17-ketosteroid excretion was 6.2 mg. per 24 hours, and several test doses of ACTH intravenously produced an adequate fall in the eosinophil count. The urinary content of lead and arsenic was within the normal range.

An electrocardiogram was normal, while electromyograms were consistent with nerve damage.

Course of the Disease: The patient's emotional instability made management difficult. Frequent enemas were needed to overcome constipation, and chloral hydrate was given for sedation. A psychiatric consultant stated that the patient had "severe neurotic conflicts concerning her femininity. . . . She is not frankly psychotic but could become psychotic. . . . She feels neglected by and hostile toward doctors. . . . She seems almost paranoid."

While in the hospital the patient was given riboflavin, 100 mg. daily. After several weeks she left the hospital against advice. Several months later the patient was given electroshock therapy elsewhere for "depression," without benefit.

Comment: The onset of the disease possibly was at eight years of age. The repeated operations are a common occurrence in patients with acute intermittent porphyria. Addison's disease was considered initially because of the pigmentary disturbance. Cortisone was ineffective in relieving the pain and weakness, and electroshock therapy failed to improve her mental status.

Case 3. A 48 year old housewife was admitted complaining of nervousness, weakness, left-sided pain and insomnia of one and a half year's duration.

In September, 1951, pain in the left buttock which radiated down the right leg caused difficulty in walking. Six months later, after taking phenobarbital for one month, the patient became apathetic. There also were generalized weakness, moderately severe lower abdominal pain, constipation and a faint voice. During months of hospitalization elsewhere the patient complained of left-sided pain, and was at times confused and hallucinated. She was improving moderately at the time of admission, but still complained of pain in the entire left side of her body, dark or hazy vision, weakness and severe insomnia.

Physical Examination on Admission: The patient was a slightly obese woman with a blood pressure of 110/64 mm. of Hg and a pulse rate of 62 per minute.

The cranial nerves were intact, and muscle power was unimpaired. The deep tendon reflexes were generally sluggish. The left knee jerk was weaker than the right, and the right ankle jerk was weaker than the left. Sensation was intact. The remainder of the physical examination was noncontributory.

Laboratory Findings: The urine was light amber in color, and the Watson-Schwartz test was positive. Uroporphyrin and coproporphyrin were also present in the urine in large amounts. After the urine was acidified it turned a dark mahogany color upon standing overnight. The hematocrit, leukocyte count, nonprotein nitrogen and serum electrolytes were all normal. Urinary 17-ketosteroid excretion was 15.9 mg. per 24 hours, and there was a drop in the eosinophil count from 169 per cubic millimeter to 0 four hours after a test dose of 25 mg. of ACTH intravenously.

Course of the Disease: Therapy consisted of 300 micrograms of vitamin B_{12} daily. The patient continued her gradual improvement and was discharged after three weeks.

Six weeks later the left-sided pain and insomnia again became severe, and the patient was re-admitted to the hospital. The pain was described as a sensation of heat and burning, followed by a painful tingling, vibrating feeling over the entire left side of her body.

The blood pressure was 132/90 mm. of Hg, and the pulse 104 per minute. The deep tendon reflexes were intact, but there was mild weakness of the left arm and hand. The only change in the laboratory findings from her previous admission was a leukocyte count of 11,350 per cubic millimeter. The Watson-Schwartz test was again positive.

The patient was given 30 units of ACTH by slow intravenous drip over a 10 to 12 hour period daily for six days, and over the next three days the dose was gradually reduced. During the ACTH therapy the patient was given a low sodium diet with potassium chloride added. On one occasion, after three days of ACTH, the patient kept her eyes closed and would not respond to painful stimuli for several hours. While she did not complain so much of pain on the left side of her body, she still complained of back pain, insomnia and weakness.

Chloral hydrate was very helpful in managing the insomnia. After 11 days the patient was discharged, only moderately improved.

Comment: Mental change and bizarre left-sided pain were the predominant features in this patient. ACTH was of little or no benefit.

Case 4. A 32 year old housewife entered the hospital on May 13, 1953, complaining of weakness of three weeks' duration.

Acute abdominal pain had occurred for the first time at 18 years of age and had lasted only a few days. During the next four or five years there were repeated episodes of vague abdominal distress, and a poor appetite.

Two years before her admission the severe abdominal pain and vomiting had recurred, and an appendectomy and a unilateral oophorectomy were performed. For the next nine months only occasional abdominal pain was noted.

In August, 1952, the abdominal pain and vomiting again recurred, and dark urine was noted. A cholecystectomy was performed, after which the patient failed to recover her strength. The weakness gradually became more severe, until the patient was completely bedfast three weeks before admission.

Physical Examination on Admission: The patient was a thin, pale woman who winced or cried out when she was touched. Her voice was high-pitched and whining in character. The blood pressure was 150/110 mm. of Hg, and the heart rate was 120 per minute. The skin over the fingers was shiny. Motor power in general was reduced, and the grip was weak bilaterally. The cranial nerves were intact. The deep tendon reflexes were brisk. Sensation was intact except for decreased perception of pinprick over the lateral aspect of the thighs and buttocks. The remainder of the examination was noncontributory.

Laboratory Findings: The urine was of a normal color. The Watson-Schwartz test was positive. Uroporphyrin and increased amounts of coproporphyrin were demonstrated in the urine. The white cell count was 4100 per cubic millimeter. The nonprotein nitrogen was 31 mg. per cent and the fasting blood glucose was 67 mg. per cent. The serum electrolyte levels were within normal limits.

Course of the Disease: The patient was afebrile throughout her hospital stay. Beginning on the fourth hospital day ACTH, 30 units, was given daily by slow intravenous drip continuously over a 10 hour period, for four days. The dosage was then gradually reduced over another four-day period. A low sodium diet with added potassium chloride was given during the period of ACTH therapy.

By the second day of ACTH therapy, muscular pain and constipation had almost disappeared and the patient's appetite had improved markedly. Graded passive and active exercises were instituted, and by the end of the second week the patient was ambulatory. On June 8, 1953, after one month of hospitalization, the patient was discharged, markedly improved. The pain and weakness have not recurred for six months.

Comment: The course of this patient's illness is similar to that of case 1. Coincident with ACTH therapy there was an abrupt, marked improvement, and the patient has continued well for six months.

Case 5. A 23 year old housewife was admitted March 18, 1944, complaining of pain in her legs of two weeks' duration.

Three years previously she had had "pain beneath the ribs" and constipation. An appendectomy was done and the patient was later told her appendix was all right but that she had "colitis."

One month prior to admission the patient awoke with nausea and vomiting. She was hospitalized for two weeks, during which time she was severely constipated and

required frequent enemas. There was gradual onset of pain and stiffness in the legs, and two days before admission weakness and trembling of the hands were noted. The patient had lost 30 pounds in one month.

Physical Examination on Admission: The patient was a thin woman complaining of pain in her arms and legs. No pigmentation or skin lesions were noted, and the rectal temperature was 99.2°. The lungs were clear and the heart was normal. The pulse was 120 per minute and the blood pressure was 150/85 mm. of Hg. On inspiration, the liver edge was palpable and was slightly tender. Emaciation of the extremities was marked.

The cranial nerves were intact, and the deep tendon reflexes were hyperactive. The patient was unable to extend the fingers of her right hand, and there was a tremor of both hands. There was also weakness of dorsiflexion of the feet. Palpation of the legs and arms revealed marked tenderness, but sensation was intact. The remainder of the examination was noncontributory.

Laboratory Findings: The urine was dark reddish brown and turned darker upon standing. The hemoglobin was 12.5 gm. per cent and the white blood cell count 9,700 per cubic millimeter. The nonprotein nitrogen was 46 mg. per cent and the fasting blood glucose 74 mg. per cent. The urea clearance was reduced by 50 per cent. The electrocardiogram was normal. A lumbar puncture revealed normal cerebrospinal fluid. An x-ray of the abdomen showed feces in the colon, and a barium enema revealed "colon stasis and spasticity." No arsenic, lead or mercury was found in the urine. Six weeks after admission a urine specimen was found to contain porphobilinogen. Two months later the urine was no longer dark and no porphobilinogen was demonstrable.

Course of the Disease: The patient became steadily weaker and complained frequently of pain in the arms and legs. She also had bouts of epigastric pain lasting up to 18 hours. Intravenous calcium gluconate partially relieved the pain in the extremities on several occasions. The blood pressure rose to 170/120 and later to 200/140 mm. of Hg.

Bilateral wrist drop and marked ulnar and median nerve paresis developed. On one occasion fluids were regurgitated through the nose, and there was a fine nystagmus on lateral gaze. In the upper extremities the deep tendon reflexes were diminished, but there was short brisk clonus in the lower extremities. No definite sensory loss was elicited, but there was marked tenderness on palpation of all the extremities.

It was discovered that the patient was pregnant, and six weeks after admission a hysterotomy was done. The fetus weighed 100 gm. After the operation the patient was given Seconal frequently for sedation. Liver extract and vitamin B were given intramuscularly, and splints were applied to the extremities to avoid contractures.

Six weeks after the operation the patient began recovering the use of her arms and legs, and improvement thereafter was rapid. On June 14, 1944, the patient was discharged with good function of her flexor muscles, while the extensors remained weak.

During the next one and one-half months the patient continued to improve. Then with the onset of her menses she began having pain in the arms, shoulders, chest and in the right lower quadrant of the abdomen. Vomiting recurred and she was re-admitted to the hospital. The patient was cheerful and coöperative, but now weighed only 68 pounds. The blood pressure was 164/114 mm. of Hg, the pulse 102 per minute and the temperature 98.6° F. There was marked atrophy of muscles, and bilateral wrist and foot drop. The nonprotein nitrogen was 44 mg. per cent and the white cell count 8,500 per cubic millimeter. A repeat lumbar puncture again revealed normal cerebrospinal fluid.

In the hospital the abdominal pain continued severe, and there was marked con-

stipation. Tube feedings were given and the patient began gaining weight after five weeks. The abdominal pain and constipation subsided and the patient was taken from the hospital by her parents.

Three months later the patient died of respiratory failure in another hospital after developing involvement of cranial nerves III, V, IX, X, XI and XII. The Watson-Schwartz test was strongly positive, and the leukocyte count was 31,050 per cubic millimeter. The electrocardiogram was within normal limits.

The postmortem findings included "slight focal degenerative changes of peripheral ganglia and nerves, pigmentation of liver, spleen, kidneys and bone marrow and extreme emaciation. There was a purulent pyelonephritis and a purulent tracheobronchitis with a lobular pneumonia."

Comment: This patient was studied in 1944, nine years ago. The pregnancy was terminated in the hope of producing a remission in her disease. (There is no evidence at this date that such a procedure is indicated.) Six weeks later the patient began improving. Her symptoms recurred coincident with the onset of the menses, and three months later she died of respiratory failure. Barbiturates are not now given to patients with acute intermittent porphyria.

TABLE 1

Clinical and Laboratory Findings in 69 Patients with Acute Intermittent Porphyria*

A. Signs and Symptoms

Number of Patients		Per Cent
First symptom related to:		
Gastrointestinal tract	49	71
Peripheral neuropathy	5	7
Mental changes	10	14
Others	5	7
Gastrointestinal symptoms	66	95
Abdominal pain	66	95
Nausea and/or vomiting	36	52
Constipation	32	46
Diarrhea	8	11
Peripheral neuropathy	53	72
Motor weakness	53	72
Absent or hypoactive deep tendon reflexes	39	56
Muscle pain	37	53
Sensory loss	17	24
Bizarre reflex change	15	22
Cranial nerve involvement	35	51
Voice change	26	37
Died	22	
Mental changes	55	80
A. Hallucinations, delirium confusion or seizures	36	52
B. Hysteria, depression, schizophrenia, paranoia	18	26
C. Irritability, restlessness	28	40
Pigmentation	9	13
Hypertension	34	49
Tachycardia	35	51
Fever	25	36

B. Age, Sex, Mortality Data, and Surgical Experience

Number of Patients		Per Cent
Male	27	39
Female	42	61
Age (at time of diagnosis)		
21–30 years	36	52
31–40 years	21	30
Dead (at time of report)	40	58
Patients operated upon	32	46
Total number of operations	48	
Appendectomy	20	
Laparotomy	13	
Pelvic	8	
Cholecystectomy	3	
Others (including nephrectomy)	4	

C. Laboratory Findings

Number of Patients	Positive	Tested
Dark or red urine	48	69
Porphobilinogen in the urine	54	54
Uroporphyrin in the urine	34	34
Leukocytosis (10,000 to 31,000)	24	50
Abnormal cerebrospinal fluid	7	31
Elevated NPN or BUN	18	27
Abnormal electrocardiogram	7	15
X-ray abnormality (GI series or flat plate of the abdomen)	12	21

* Including 64 patients collected from the literature and five cases reported here.

Symptoms and Signs

It is evident from table 1 that the symptoms fall into the classic triad of (1) abdominal pain, (2) peripheral neuropathy, and (3) mental or psychic changes. At some time during the course of the disease all but three patients had abdominal pain, over three fourths had mental or psychic changes of varying severity, and three fourths had a peripheral neuropathy.

The initial complaint of 49 patients was abdominal pain. Only 10 patients had mental or psychic changes as their first symptom, and in five patients the disease began with weakness. Other initial symptoms mentioned were dysuria, toothache and pain in the throat.

Gastrointestinal Symptoms: Severe, colicky abdominal pain was the major gastrointestinal symptom. This pain may mimic that seen in any acute surgical emergency and may last hours to months. Characteristically, the physical findings do not support the diagnosis of a surgical emergency. The patients may complain of tenderness on palpation, but there is no rebound tenderness, and the abdomen is soft.

Nevertheless, all five of our patients had had at least one pelvic operation and an appendectomy. Watson [2] reported one individual who had had 10 laparotomies over an eight year period. In this series of 69 patients, 32 had been operated upon a total of 48 times, with appendectomy or laparotomy accounting for almost 80 per cent of these. There were several instances of cholecystectomy and of unilateral nephrectomy. The great majority of the operations would not have been performed had the correct diagnosis been made. Calvy [62] recently stressed the significance to the surgeon of acute intermittent porphyria.

Nausea or vomiting or both accompanied the abdominal pain in 36 of the patients, and constipation was specifically mentioned in 32. Waldenstrom [3] thought constipation was probably always present, but he also noted eight patients who had diarrhea. In the 69 patients reviewed here, only eight had diarrhea, or diarrhea alternating with constipation.

Peripheral Neuropathy: Motor symptoms which varied from weakness to quadriplegia were reported in over 75 per cent of the patients. The weakness may begin anywhere, and it progresses unpredictably. The older literature speaks of Landry's ascending paralysis as being a characteristic finding. This was first denied by Waldenstrom, and in this series was noted only six times. Several references point to the almost "functional" appearance of the weakness—as though the patients could overcome it if they tried.

In 39 patients of this series, the deep tendon reflexes were lost or hypoactive. They could be present one day and absent the next, only to reappear later. Roth [50] has stressed the variability of the deep tendon reflexes. He noted that the quadriceps reflex might be absent while the achilles reflex was brisk. Similar bizarre reflex change was noted in 15 instances, including two of our patients.

The weakness and deep tendon reflex changes may persist for prolonged

periods and still be followed by complete recovery. One of our patients was quadriplegic and had marked atrophy of the muscles of her extremities and yet, when she was seen over two years later, only a mild foot drop remained.

Sensation has previously been reported as being intact, but in this series minor sensory loss usually limited to diminished perception of pinprick was described in 17 patients. The sensory examination was, however, very difficult to evaluate because of the severe muscle pain and tenderness on palpation noted in 55 per cent of patients.

The muscular pain was often described as burning or aching in character and was occasionally the chief complaint. One of our patients had bizarre pain over the entire left side of her body.

Mental or Psychic Changes: Mental or psychic changes were present in all five of our patients and in over three fourths of the patients reported in this series. Minor changes such as irritability, tiredness or restlessness occurred in 28 patients. In 36 instances hallucinations, delirium, confusion or epileptiform seizures were noted. In 18 patients a diagnosis of hysteria, schizophrenia, depression or "paranoia" was made.

Three of the five patients admitted here had been referred to psychiatrists prior to admission. The irritability, noisiness and demanding attitude of these patients made them difficult to manage. Three of our five patients left the hospital against medical advice.

Cranial Nerve Involvement: Thirty-five of the patients had cranial nerve involvement which varied from mild vocal cord paresis to respiratory failure and death. There was no report of cranial nerve involvement without peripheral nerve involvement.

The high-pitched whining voice was a striking feature in three of our patients. This change probably resulted from vocal cord paresis, and possibly also from the psychic change. In the entire series, vocal changes of some type were noted in 26 patients.

Vital Signs: Thirty-four patients exhibited a hypertension of 150/100 mm. of Hg or above, and an equal number had a tachycardia. Since in many instances the blood pressure and pulse rate were not recorded during the acute phase of the disease, it is probable that hypertension and tachycardia occurred even more frequently.

Fever, almost always low grade, was noted in over one third of the patients at some point in the course of the disease. In many instances this may have been due to secondary infection. Many case reports specifically denied the presence of fever during the early acute phases of the disease.

Brown pigmentation of the skin was noted in nine patients. One of our patients had small spots of brown pigment on her buccal mucosa and Addison's disease was seriously considered. Jaundice was also reported several times.

Laboratory Findings: Urine: Three of our five patients had dark urine, and this was also noted in 70 per cent of the entire series.

The Watson-Schwartz test (or other tests) for porphobilinogen was positive in 54 patients, or almost 80 per cent. In the remaining patients uroporphyrin was demonstrated in the urine.

Blood: A leukocytosis of 10,000 to 31,000 per cubic millimeter was reported in 24 patients. This may have been a further confusing factor which led to laparotomy in the acutely ill patients with abdominal pain.

The nonprotein nitrogen or blood urea nitrogen was elevated in 18 of the 27 patients in whom it was reported. In several instances oliguria during the acute episode, or superimposed urinary tract infection, may have been a factor in the elevated nonprotein nitrogen level.

Sterling, Silver and Ricketts [45] recently reported the coexistence of porphyria with diabetes mellitus and raised the question of the rôle of diabetes in the causation of porphyria. None of our patients had an elevated fasting blood sugar level. Only three patients in the entire series had fasting blood glucose levels above 100 mg. per cent.

Several British authors [11, 12, 13] described patients with low serum or chloride levels. Treatment with adrenocortical hormones failed to raise the sodium and chloride levels. None of our patients showed any abnormality in their serum electrolytes. In addition, three of our patients showed an adequate eosinophil response to a test dose of ACTH, thereby indicating adequate function of the adrenal cortex.

The cerebrospinal fluid was reported as normal in 24 patients and abnormal in only seven. In general, the abnormality was mild, i.e., 5 to 10 cells per cubic millimeter or mildly elevated protein content. However, in one patient the cerebrospinal fluid changes mimicked a purulent meningitis.[44]

Electrocardiographic changes restricted to nonspecific lowering of the T waves, or ST segment depression or both,[57] were noted in seven patients. The electrocardiogram was normal in 8 patients and was not reported in the remainder.

Electromyographic studies were compatible with those seen in regenerating peripheral nerve injuries. Peters [34] reported one patient in whom many severely affected muscles recovered almost to normal. One of our patients (case 1) showed poor faradic response in the median and ulnar nerves and no faradic response in the radial and femoral nerves. Case 2 showed fibrillating voltages and complex units on volitional effort, indicating axonal degeneration in the right ulnar nerve.

Electroencephalograms: Coffman and Kuhl [47] report the electroencephalographic finding of a toxic encephalitis in their patient.

X-ray: The x-ray findings in acute porphyria were recently reviewed by Berlin and Cotton,[41] Fisher and Stanley [42] and Calvy and Dundon.[43] The findings, again nonspecific, included slow passage of a barium meal, dilated loops of small or large bowel, impacted feces, and atony of the esophagus or duodenum. Occasionally, fluid levels were found suggestive of intestinal obstruction.

In 12 case reports in this series such findings were noted, while in nine, x-rays of the gastrointestinal tract were normal.

Pathogenesis

Waldenstrom [5] observed many families in which a number of individuals had acute intermittent porphyria, and concluded that the disease was transmitted as a mendelian dominant. Among the 69 patients reviewed there was either a proved or a suspected family history in 11 instances. The family history was negative in 17 cases, and not mentioned in the remaining 41.

Only three Negroes are included in this review. One was living in England,[40] one in New York,[38] and the third was a Bantu native living in Africa.[39] There were no reports of patients of the other pigmented races.

Previous reports [1, 5, 6] have shown a preponderance of women in a ratio as high as four to one. All five of our patients were women, but in the entire series there were 42 women and 27 men, which is approximately a 3 : 2 ratio. The menses, or pregnancy, coincided with the onset of an acute exacerbation of porphyria in 19 patients. It is not clear whether this is mere chance or a pathogenetic factor. On the other hand, one patient improved during and following a pregnancy,[46] and one of our patients (case 5) improved transiently after hysterotomy and removal of a six week fetus. Her symptoms then recurred when her menses recommenced.

Forty-five per cent of the patients were 21 to 30 years of age at the time of the diagnosis of acute intermittent porphyria, and 70 per cent were between 21 and 40 years of age. The estimated age at the onset of the disease was between 21 and 40 in 80 per cent of the patients. The earliest estimated onset was at eight years of age, while the latest was in the sixth decade.

The factor or factors producing an acute episode of porphyria are unknown. Waldenstrom [5] indicted drugs as a factor, and he cited instances in which barbiturates apparently produced exacerbations of acute intermittent porphyria. However, other patients have recovered while taking barbiturates regularly. In this series barbiturates were given to 22 patients at some point in the course of their illness. Sulfonamides were given to seven patients and, in one instance, the onset of symptoms coincided with the administration of chloroquine given for amebiasis.[16] Many other drugs have been incriminated, including arsenic, lead and other heavy metals. In animal experiments, Sedormid has produced porphyrinuria.[63, 64]

The relationship between the pathologic metabolites and the clinical symptoms is also not clear. In this respect, Waldenstrom compared porphyria with gout,[5] in which the significance of the uric acid level to the course of the disease is equally unknown. In animal experiments, loops of bowel bathed in porphyrin solution go into spasm which is not relieved by atropine. Watson, on the other hand, injected relatively large amounts of coproporphyrin into human volunteers without creating any symptoms.[2]

Porphobilinogen is not found in the urine of patients with porphyria hematopoietica, and these patients do not have the abdominal pain and nervous system involvement which is seen in acute intermittent porphyria. Patients with chronic porphyria may have porphobilinogen in the urine when they have abdominal pain. Watson [2] suggested that the symptoms were therefore caused by porphobilinogen, although at present supportive data are lacking. Instances have been reported in which patients had no porphobilinogen or uroporphyrin in the urine during an acute exacerbation of the disease and then later, during recovery, these substances appeared.[5] Also, in spite of the continued excretion of porphobilinogen in the urine, a patient may be asymptomatic. One of our patients (case 1) almost completely recovered from quadriplegia and had no further episodes of pain, but two and a quarter years later the Watson-Schwartz test for porphobilinogen was still strongly positive.

Denny-Brown and Sciarra [28] noted that the lesions produced by experimental pressure ischemia resembled the degenerative changes found in the spinal cord and peripheral nerves of patients who died of acute intermittent porphyria. Several patients with transient blindness during an acute episode of the disease were described by Waldenstrom,[5] and Denny-Brown saw beading of the retinal arterioles in one patient.[28] Retinal arterial spasm was mentioned only three times in this series.[14, 15, 51]

Berlin and Cotton [41] suggested involvement of the parasympathetic nervous system in acute intermittent porphyria. They based this suggestion on the similarity of the findings seen on the x-rays of the gastrointestinal tract in acute intermittent porphyria to the x-ray findings seen after vagotomy.

The porphyrins in acute intermittent porphyria are excreted as a zinc complex. To rule out excessive loss of zinc as a cause of the symptomatology, Nesbitt [7] measured the zinc content of liver and pancreas in a patient who died of the disease and found it to be normal.

Finally, psychic trauma has been advanced as an etiologic factor in this disease.[50]

Diagnosis

Patients with acute intermittent porphyria have been mistakenly diagnosed as combat fatigue, hysteria, pheochromocytoma, appendicitis, glomerulonephritis, Addison's disease, cholecystitis, bowel obstruction, epilepsy, poliomyelitis, muscular dystrophy and delirium tremens. Even though there is no specific treatment for this disease, the diagnosis should be made as early as possible to avoid unnecessary surgical procedures and exposure to drugs which might precipitate exacerbations of the diseases.

To make the diagnosis, the "index of suspicion" must be high. The possibility should be thought of in patients having the following: abdominal pain with minimal physical findings, a peripheral neuropathy of any type,

and continued psychoneurotic symptoms. A history of many laparotomies with persistence of pain or the passing of dark red urine is suggestive.

Once the diagnosis is thought of, the Watson-Schwartz test for porphobilinogen can be done rapidly. If it is positive, and the patient is not photosensitive, it almost certainly indicates acute intermittent porphyria. Further studies can then be done to determine the types of porphyrins present in the urine. The demonstration of uroporphyrin of Waldenstrom type in the urine is diagnostic of the disease.

Pathology

A considerable number of necropsies have been reported but with disappointingly nonspecific findings. Little new has been added since the review of the pathologic findings by Mason et al. in 1933.[1]

The major findings are in the nervous system and consist of a patchy degeneration of the myelin sheaths of the peripheral nerves and chromatolysis of the anterior horn cells of the spinal cord. Abbott and Evas [20] noted that the myelin degeneration was most severe where the sheaths entered the central gray matter of the cord, and in the intracortical portions of the cerebral cortex. Because the blood supply is best in these areas, this suggested to them a toxic factor carried by the blood stream.

Varied degenerative changes have been described in the Purkinje cells of the cerebellum, and also in cells of the dentate nucleus, cerebral cortex, basal ganglia, hypothalamus and in the celiac ganglion. Others have been able to demonstrate changes in the peripheral nerves but not in the brain or spinal cord. The extent of the changes probably depends, in part, on the duration of the disease.

Prunty [30] described early necrosis of the centrilobular liver cells, and two types of granular pigment in the liver: the first, large and small golden yellow granules; the second, small orange-red granules. Very little iron pigment was present. The kidney tubules were lined with a red fluorescing material under ultraviolet light. By this same method, red fluorescence was also seen in the liver, central nervous system, costal cartilages, posterior pituitary, adrenals, heart and sternal marrow.[30, 29, 40]

Treatment

There is no specific therapy for acute intermittent porphyria. Spontaneous remissions and the great variability of the disease make the evaluation of any therapy difficult. Since the B vitamins are a part of some porphyrin-containing enzyme systems, they were among the first to be tried. The latest enthusiasm was for the use of massive doses of riboflavin. However, Watson [2] reported that riboflavin had no beneficial effect. Vitamins C, E, B_{12}, and liver extract have also been ineffective. Because the patient's weakness sometimes mimicked myasthenia gravis, Prostigmin was given. The only benefit noted was in speeding the passage of a barium meal.[41]

Grubschmidt [37] gave intravenous procaine to one patient during several episodes of abdominal pain, with good relief of the pain each time. Cobra venom in the same patient was not effective.

Calcium salts were advocated, presumably because calcium combines with porphyrin to form an insoluble salt. Results reported are variable but in the main discouraging. Magnesium sulfate, intravenously or intramuscularly, has also been advocated for the relief of pain.[32] Atropine has failed to relieve the abdominal pain. Many patients in this series were given narcotics, usually morphine, for relief of their pain, with good result.

The use of ACTH or cortisone has been reported in six patients with porphyria. Five [14, 15, 16, 12] are included in this series, but the sixth [17] was excluded because the patient was photosensitive. Gilbert, Toupin and Bell [14] gave cortisone to one patient. Thirteen days after therapy was begun the patient's pain and constipation ceased and his appetite increased. Three weeks later, while he was still receiving cortisone, the symptoms recurred and he died despite continued cortisone medication. Porphyrin excretion fell from 4400 μg./day before cortisone to a level between 184 and 227 μg./day, but later rose to 6000 μg./day while cortisone was still being given. However, the transient decline also coincided with the withdrawal of phenobarbital.

Wheeler [15] treated one patient with 12.5 mg. of ACTH by slow intravenous drip over a seven to eight hour period for four days. There was no immediate change in the patient's condition. Later, however, the patient improved.

Myerson [16] treated one patient with ACTH and stated it had no effect upon the excretion of coproporphyrin. This patient also had carcinoma of the lung and later died.

Goldberg, MacDonald and Rimington [12] treated one patient with aqueous adrenocortical extract and with desoxycorticosterone acetate without any effect on the low serum chloride level. A second patient was given 12.5 mg. of ACTH intramuscularly every six hours for one week. Within two days the patient's general condition improved and he became euphoric. Before ACTH therapy, the uroporphyrin excretion in the urine had been 15 to 37 mg./day. On the third day of ACTH therapy 120 mg. of uroporphyrin were excreted, and thereafter approximately 5 μg. per day. They state, however, that further experience with ACTH revealed no alteration of uroporphyrin excretion.

Three of our patients were given cortisone or ACTH. Case 2 was given a two week course of cortisone (before we saw her) as therapy for her supposed rheumatoid arthritis, without benefit. Cases 3 and 4 were given ACTH, 25 to 30 units by intravenous drip over an eight to 10 hour period daily for four to six days. The dosage was then reduced over the next three to four day period. While receiving ACTH both patients were on diets low in sodium, and with 3 gm. of potassium chloride added daily. Case 3 continued to complain of insomnia and weakness, but her left-sided

pain may have been partially relieved. On the third day of therapy the patient had one episode resembling hysteria which lasted several hours, during which time her eyes were closed and she would not respond to painful stimuli. ACTH seemed of little or no benefit to this patient. Case 4 responded quite dramatically to ACTH therapy. The constipation and generalized muscular pain ceased within 48 hours and her appetite and general outlook improved greatly. Recovery thereafter was rapid. However, this patient had improved moderately before ACTH was begun. Table 2 shows the daily urinary uroporphyrin and coproporphyrin excretion of case 4 before, during and after ACTH therapy. The quantities of porphyrins excreted vary so greatly from day to day that many such observations will have to be made before any conclusions can be drawn.

TABLE 2

Urinary Uroporphyrin and Coproporphyrin Excretion in Mg./24 Hours Before, During and After ACTH (Patient 4)

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
ACTH (in units)	0	0	30	30	30	30	20	10	10	5	0	0	0	0	0
Uroporphyrin	1.35	2.64	8.35	0.74	3.38	6.73	5.15	—	—	—	—	—	4.12	3.8	1.96
Coproporphyrin	2.76	5.46	2.78	1.35	2.98	6.27	4.32						1.7	1.34	1.6

The benefit of ACTH may be due only to the increase in appetite and euphoria. However, Watson [2] stated that he knew of three instances of a dramatic response to ACTH by acutely ill patients, and he concluded that seriously ill patients deserve a trial with ACTH.

Electroshock therapy (EST) has been given to four patients with acute intermittent porphyria who were considered to be psychotic.[25, 48, 49] Freeman and Kolb's [48] patient was the only one who showed improvement. However, before therapy began, porphobilinogen had disappeared from the urine. Two other patients [25, 49] treated with EST failed to improve. One of our patients (case 2) was treated elsewhere with EST for "depression," without benefit.

Routinely, we have warned our patients against taking any barbiturates, sulfonamides or heavy metal medication. Graded passive and active exercises and hydrotherapy have proved useful in aiding the return of muscular function. Chloral hydrate and paraldehyde have been used for sedation. Morphine, Demerol and codeine have been effective in the relief of pain. A high caloric, high vitamin diet was given to all of our patients who were undernourished.

PROGNOSIS

Waldenstrom stated that there was no other metabolic disease with so serious a prognosis as acute intermittent porphyria.[8] He divided his patients into various groups according to their symptoms and compared the mortality in each group. Twenty patients with latent porphyria all lived.

Twenty-four patients had only abdominal symptoms, and 20 of these survived. Of 49 patients with nervous system involvement, 42 (86 per cent) died. In another grouping of 47 patients with acute porphyria, 35 died. Of these 35, 20 lived less than one year after the onset of their disease. One patient, however, died of an intercurrent infection 35 years after the beginning of his illness. Of the 12 surviving patients, seven had been followed three years or less, but one was still living 27 years after the first episode of the illness. The over-all mortality in Waldenstrom's 100 patients was 52 per cent.

In the present series of 69 patients, the over-all mortality was 58 per cent. The greatest mortality, 63 per cent, was among those patients with cranial nerve involvement. Only one of the 15 patients with no peripheral or cranial nerve involvement was dead at the time of the report.

Since many patients had repeated episodes of abdominal pain over the course of many years, it is apparent that the mortality during any one episode of abdominal pain is quite low. However, involvement of the central nervous system, especially of the cranial nerves, indicates a much more serious prognosis, with a mortality ranging from 60 per cent to 90 per cent.

Summary

1. The symptomatology and laboratory findings in 64 patients with acute intermittent porphyria reported from 1941 to 1953 are reviewed.

2. Five cases of acute intermittent porphyria are reported.

3. The pathogenesis and pathology of the disease are briefly reviewed.

4. Treatment is discussed, particularly with reference to the use of ACTH or cortisone.

5. The prognosis is particularly grave when there is cranial nerve involvement. In such patients, the mortality is 60 to 90 per cent.

6. The diagnosis should be suspected in patients with abdominal pain, peripheral neuropathy and mental or psychic changes. Chemical proof of the diagnosis depends on the demonstration of uroporphyrin or porphobilinogen in the urine.

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THE MANAGEMENT OF MYOCARDIAL INFARCTION WITH PARTICULAR REFERENCE TO THE CHAIR TREATMENT *

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THE time-honored treatment of acute myocardial infarction at complete bed-rest has been challenged recently and evidence presented that many patients do at least as well if allowed to sit in a chair during their convalescence as they would if confined strictly to bed.[1, 2, 3] It has been previously pointed out that there are many disadvantages to complete bed-rest,[4, 5] and a recent review emphasizes how its abuse unfavorably [6] affects the cardiac patient. There is also evidence which indicates that the cardiac work is greater when an individual is lying in bed than when he is sitting in a chair.[7]

In order to compare the bed-rest treatment with the chair treatment, alternate patients with acute myocardial infarction, admitted to the hospital, were treated at rest strictly in bed or in bed part of the day and in a chair by the bedside at intervals during the day.

METHODS AND MATERIAL

The series consisted of 80 consecutive admissions to the hospital of patients with acute myocardial infarction who had lived 24 hours or more. The diagnosis was made by clinical study including 12-lead electrocardiograms. Five patients were found to have left bundle branch block, in three of whom the changes of infarction were obscured by the block, but the clinical findings were typical and consequently these three patients were included in the series.

All patients were given an anticoagulant, Dicumarol or Tromexan, and prothrombin time determinations were performed once or twice daily. An effort was made to keep the prothrombin time from two and a half to three times that of a normal control done simultaneously.

All patients remained in the hospital for 28 to 38 days. They were given morphine or Demerol to control pain and were placed on a diet limited in calories. The orthodox methods for the management of heart failure

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were employed when it occurred. Oxygen was administered to most of the patients during the first 48 hours after admission and to all who had severe pain, shock or heart failure.

Alternate patients, who were treated in a chair, are referred to herein as "Up Patients," and those confined to bed as "Down Patients." Two Up Patients who were diagnosed on admission as having myocardial infarction were thought later not to have this condition and therefore were not included in the series, making 39 in the Up Patient group and 41 in the Down Patient group. The Up Patients were allowed in a chair for increasing lengths of time from the second to the fifth day after the infarction. No patient was allowed up until shock, if present, had been controlled or pain had almost disappeared. The following schedule was followed in allowing these patients up:

30 minutes three times a day for three days.
60 minutes three times a day for three days.
90 minutes three times a day for six days.

Then they were allowed up at will until 28 days had elapsed since the onset of the infarction. They were carefully assisted to the chair and back to bed. The chair was a comfortable arm-chair with adequate back support which did not allow pressure on the popliteal spaces. These patients were allowed to use a bedside commode or, in several instances, to walk a few steps with assistance to the bathroom once daily.

The Down Patients were kept in bed for 28 days and were not allowed to bathe, shave or feed themselves until the second week after the infarction. They were encouraged to flex and extend their feet frequently, and several were allowed use of a bedside commode once daily. All patients were classified as Good Risks or Poor Risks according to the presence of one or more of the following conditions during the first three days after the onset of the infarction:

Poor Risks:

- History of a previous infarction
- Presence of intractable pain
- Presence of heart failure
- Occurrence of an arrhythmia such as
  - Paroxysmal auricular tachycardia
  - Auricular fibrillation
  - Auricular flutter
  - Frequent ventricular ectopic beats from more than one focus
  - Ventricular tachycardia
  - Heart block
- History or presence of thromboembolic phenomena
- Greatly enlarged heart

This classification is similar to that described by Russek et al.[8] except that in the present series the patients were not classified until three days after the infarction had developed.

All others not having any of these features were considered Good Risks.

Results

Table 1 shows the different age groups of the Up and Down Patients. The incidence of Good Risks and Poor Risks in the two series is also shown.

Table 1

Age Group	30–39	40–49	50–59	60–69	70–79	80–89	Total	Good Risks	Poor Risks
Up	0	9	10	14	4	2	39	20	19
Down	2	9	8	16	5	1	41	22	19

The total mortality and the mortality of the Good and Poor Risks are seen in table 2. There were three deaths in the Up Group, a mortality of 7.1 per cent. One of these was a Good Risk and two were Poor Risks. The mortality of the Good Risks was therefore 5.0 per cent, and that of the Poor Risks 10.6 per cent.

Table 2

Mortality

	Total	No. Died	% Mortality	Good Risk	No. Died	% Mortality	Poor Risk	No. Died	% Mortality
Up	39	3	7.7	20	1	5.0	19	2	10.6
Down	41	6	14.7	22	2	9.1	19	4	21

Six deaths occurred in the Down Patient group, a mortality of 14.7 per cent. Of these, two were Good Risks and four were Poor Risks. The mortality of the Good Risks in the Down Patients was 9.1 per cent, and of the Poor Risks 21 per cent.

Thromboembolism: It can be seen in table 3 that two incidences of thromboembolism occurred in each group. In three of these four patients

Table 3

Thrombo-embolic Phenomena

	Up	Down
Extension of original infarction	2	1
Cerebral embolism	0	1
Phlebothrombosis	0	0
Peripheral embolism	0	0
Total	2	2
Died	1 (extension)	1 (extension)

Prothrombin time was satisfactory in three of the four. It was unsatisfactory in one Up Patient who died following extension.

the prothrombin time was within a suitable therapeutic range at the time. In one who died following an extension of the original thrombosis it was unsatisfactory. The other death associated with thromboembolism occurred in the Down Group. It should be noted that there was no incidence of peripheral arterial embolism in either group. Early ambulation has been suggested as a cause of this complication.[9]

TABLE 4

Arrhythmias

	Total	No. Died	%
Up	15	2	13.3
Down	15	2	13.3

Arrhythmias: Table 4 shows that 15 of the Up Patients and 15 of the Down Patients developed arrhythmia, with two deaths in each group. One Up Patient who developed paroxysmal auricular tachycardia and one with ventricular ectopic beats died. One Down Patient with complete heart block died, and the other death resulted from ventricular tachycardia.

In table 5 the incidence of the various arrhythmias in the two series is given.

TABLE 5

Type and Incidence of Various Arrhythmias

	Up	Down
Ventricular ectopic beats	9	10
Ventricular tachycardia	0	1
Auricular ectopic beats	5	3
Auricular fibrillation	3	1
Paroxysmal auricular tachycardia	1	0
Sino-auricular block	1	0
Partial AV block	2	0
Complete AV block	0	2

Heart Failure (table 6): Heart failure occurred in 10 of the Up Patients, with two deaths, and in six of the Down Patients, with one death, a mortality of 20 per cent and 16.6 per cent, respectively.

Previous Myocardial Infarction (table 6): It was established that a previous myocardial infarction had occurred in five of the Up Patients and in 11 of the Down Patients. None of the former but two of the latter died.

Shock (table 6): Shock was considered to be present if the patient's blood pressure dropped to 90 or below systolic and he presented the classic

TABLE 6

	Heart Failure			Previous Myocardial Infarction			Shock		
	No.	Died	% Mortality	No.	Died	% Mortality	No.	Died	% Mortality
Up	10	2	20	5	0	0	6	0	0
Down	6	1	16.6	11	2	18	6	3	50

picture of shock, that is, sweating, pallor, narrow pulse pressure and tachycardia, although occasionally bradycardia was present. Six patients in each group were thought to have shock. None of these in the Up Patient group died, while three in the Down Patient group died.

TABLE 7

Prothrombin Time

	Up	Down
Satisfactory	31	32
Unsatisfactory	8	9

Prothrombin Time (table 7): The prothrombin time was constantly in a satisfactory therapeutic range in 31 of the 39 Up Patients and in 32 of the 41 Down Patients. Of those who did not have satisfactory levels, one died in each group. Therefore, it would seem unlikely that differences in anticoagulant therapy would bear on differences in Up or Down results.

Analysis of Deaths (table 8): Of the Up Patients, two were Poor Risks and died with heart failure. One died following an extension of the original

TABLE 8

Analysis of Deaths

	Up Patients			Down Patients					
Day after Infarction	21	24	8	5	11	18	12	27	23
Cause of Death	Extension	Failure	Failure	Complete Heart Block	Sudden	Sudden	Failure	Ventricular Tachycardia	Sudden
Classification	Good Risk	Poor Risk	Poor Risk	Poor Risk	Poor Risk	Good Risk	Poor Risk	Good Risk	Poor Risk

infarction, at which time the prothrombin time was unsatisfactorily low. Of the Down Patients, four were Poor Risks and two were Good Risks. One died with complete heart block, one with ventricular tachycardia, one with heart failure, and three died suddenly and unexpectedly, probably with ventricular fibrillation.

COMMENT

It was difficult to measure the psychologic benefit which the Up Patients experienced, but it was quite apparent to all observers that the patients in this group were much less apprehensive and less depressed. This decrease in anxiety has an advantage, as demonstrated by Stead et al.[10] The patients seemed to take an active interest in their recovery and to feel that they could look forward to a future of reasonable activity. When they were discharged from the hospital, rehabilitation was well in progress. This psychologic advantage was enhanced by the fact that constipation was less trouble-

some and there was less trouble with urination. Muscle tone was better and there was a more general sense of well-being.

The Down Patients, however, were frequently depressed, and when the four-week period of bed-rest was completed rehabilitation, which was well advanced in the Up Patients, was just beginning.

The age distribution in the two groups seems to be fairly comparable, and it appears that the severity of the disease is about the same, since the number of Good and Poor Risks is about equal. The increased mortality among the Poor Risks of each group would seem to attest to the validity of the method of classification, although admittedly such a classification has inherent limitations.

The total mortality of the Up Patients was 7.7 per cent, against 14.7 per cent in the Down Patients. This difference is difficult to evaluate because of the small number of patients involved and the lethal potency of some of the factors involved. For example, the difference in mortality of patients with shock is striking but unexplained, except that the degree of shock and its total effects vary beyond clinical prediction or explanation.

There was no marked difference in the incidence of heart failure, thromboembolism or arrhythmia which would point to any advantage or disadvantage for either method of management.

A recent review has indicated that ventricular aneurysm is more apt to occur in patients who have inadequate bed-rest after acute myocardial infarction.[11] It should be emphasized that the Up Patients in this report were *not allowed early ambulation*, but that they were allowed to rest in a chair rather than in bed. It would seem that the danger of aneurysm might really be less in these individuals, since the cardiac work is less in individuals sitting quietly in a chair than in the same individuals lying in bed.[7]

Summary

1. A series of 80 patients with acute myocardial infarction is reported. Alternate patients were treated in a chair and at bed-rest. There were 39 Up Patients and 41 Down Patients.

2. Three of the Up Patients and six of the Down Patients died, a mortality of 7.7 per cent and 14.7 per cent, respectively.

3. The two groups were reasonably comparable as to age and severity.

4. The chair treatment apparently did no harm and seemed to be attended by psychologic and physical benefits.

Conclusion

Despite the relatively small series of patients reported, it appears safe to state that patients with myocardial infarction can be treated with daily episodes of rest in a chair after the disappearance of shock and pain.

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THE CONTROVERSIAL USE OF CERVICAL SYMPATHETIC BLOCK IN APOPLEXY *

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INTRODUCTION

IN 1948, the late Dr. N. C. Gilbert and I reported a small group of patients suffering from apoplexy in whom the cervical sympathetic trunk was blocked on the side of the lesion.[1] Return of consciousness and of speech, motor improvement and conversion of flaccid to spastic paralysis were observed in some of these patients. We suggested a less passive attitude toward the treatment of acute cerebral vascular accident.

The method previously suggested for this purpose by Leriche and Fontaine,[2a] Mackey and Scott [2b] and Volpitto and Risteen [2c] had not created much interest, but following our communication in the *Journal of the American Medical Association* a loud chorus of opposition became audible. It would seem timely now to summarize the evidence against and for this procedure and to assign a place, if possible, to the use of cervical sympathetic block in the treatment of apoplexy.

ARGUMENTS AGAINST THE METHOD

Many of these arguments have already been mentioned in our first article and more have since accumulated. These can be listed under the following headings:

1. The vasomotor control of cerebral vessels is weak, and constrictor activity in the vessels of the pia mater is about one tenth of that of the skin.[3]

2. While extremities have a highly fluctuating vasomotor tone, the cerebral vessels do not engage in heat regulation, and many safeguards—predominantly the carotid sinus and the aortic depressor mechanisms—are developed to maintain as even a total blood flow as possible.[4]

3. The vessels of the pia have been seen to contract in experimental embolism, and this vasoconstriction could be abolished by cervical sympathetic block.[5] These observations, however, relate to the superficial vessels and do not reveal any information regarding the reactivity of the intracerebral vascular tree.

4. Section of the cervical sympathetic trunk in the animal results in an increase in blood flow in the extracranial regions, such as neck, face and ears, with no change in the intracranial region.[6]

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5. Bilateral stellate block does not significantly affect cerebral blood flow or cerebral vascular resistance in normal or hypertensive individuals.[7]

6. The vasodilator effects of increased CO_2 or decreased O_2 are definite; general vasodilators such as histamine, acetylcholine and nicotinic acid show a measurable increase in cerebral circulation, in contrast with the effect of sympathetic block.[8]

7. A series of clinical reports deny any improvement in the state of patients affected by apoplexy. Others show evidence that transient states of paralysis are not on a vasospastic basis and that cerebral angiospasm is a nonexistent clinical entity.[9]

Arguments in Favor of the Method

1. Clinical reports indicating an early improvement of neurologic signs and symptoms following the use of sympathetic block.[1, 2, 9]

2. Decrease in cerebral vascular resistance after cervical sympathectomy.[10]

3. Postmortem evidence that in 60% of the cases of cerebral infarction there was no mechanical occlusion of cerebral vessels by embolism, thrombosis or arteriosclerosis, and in only a few patients was there shock or heart failure, thus pointing to vasoconstriction as the cause of ischemia.[11]

4. Increased vascularity of the brain after cervical sympathectomy as revealed by angiography.[12]

5. Production by cervical sympathetic stimulation in animals of increased vasomotor tone ipsilateral to stimulation and diversion of extracranial blood to intracranial vessels, with consequent dilatation of vessels opposite the excitation.[13]

The Vasomotor Apparatus in Apoplexy

One can readily agree that the vasomotor control of the brain is less active than that of the skin, and it is quite probable that pial vessels have higher vasomotor tone than intracerebral ones. One is also impressed with the fact that many patients derive no benefit after nerve injection, and that most of the time angiospasm cannot be proved. Let us discuss for a moment, however, the mechanism by which vasomotor paralysis of the brain could be beneficial in certain types of cerebrovascular accidents.

Certain types of stroke occurring in brain tumors, in subdural, subarachnoid and intracerebral hemorrhage are obviously not suitable for this treatment and need immediate neurosurgical consultation.[14] This leaves us, then, with the small group of emboli which are usually easy to diagnose, and the large group of cerebral infarcts which may be anemic or hemorrhagic. As pointed out by Hicks and Warren,[11] the fundamental process is ischemia, but the initial mechanism may vary from a carotid artery occlusion to a thrombus in the middle cerebral artery, and yet manifest itself in a hemor-

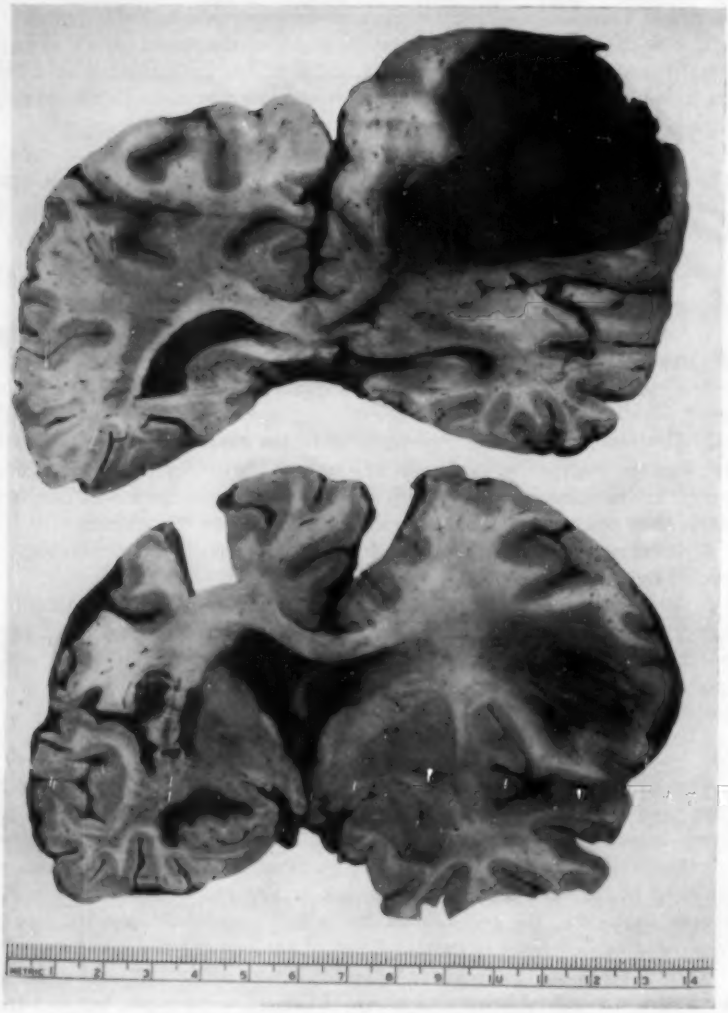

FIG. 1. This 44 year old St. Luke's nurse, C. W., had been admitted several times to the hospital with rheumatic heart disease, auricular fibrillation and cerebral embolism, from which spastic paralysis resulted. On her last admission she was again regarded as having a cerebral embolism with a negative spinal fluid. At autopsy a massive intracerebral hemorrhage was seen, together with old areas of encephalomalacia and many recent punctate hemorrhages. St. Luke's Hospital Autopsy 41 : 1941.

rhagic apoplexy with blood-tinged spinal fluid or even a massive intraventricular hemorrhage. A case in point is that of C. W., a 44 year old St. Luke's nurse who was treated with multiple sympathetic blocks with transient benefit after each injection. Her spinal fluid was negative at first and was not repeated until the tenth day, when it was frankly bloody. At autopsy

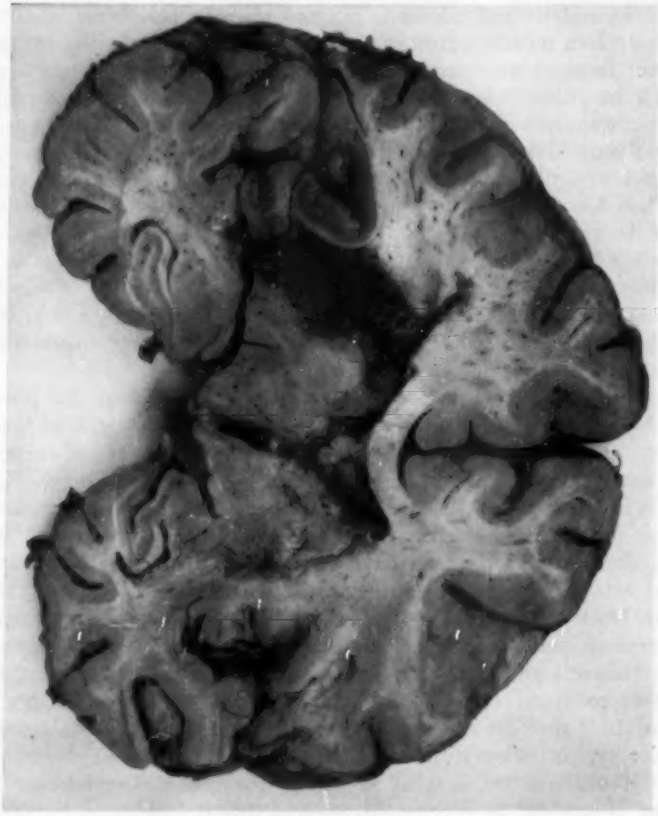

FIG. 2. Thrombosis of the right internal carotid, right middle and anterior cerebral arteries, with slow onset of blindness in left eye, optic disc atrophy and aphasia. Collateral circulation from opposite side must have been active. Autopsy 271, 1945.

a massive confluent hemorrhage was found in the left hemisphere, with many punctate hemorrhages surrounding it (figure 1). Hicks and Warren were impressed by the fact that emboli or thromboses often present hemorrhagic infarcts, and that in 60 autopsies out of 100 no arterial occlusion could be found to account for the cerebral infarct. Such findings throw grave doubt

upon the accuracy of differentiating hemorrhage from thrombosis or embolism (figure 2). I would not be so positive today about these diagnoses. In fact, just as a myocardial infarct is a more secure diagnosis than a coronary thrombosis, so it might be wise to speak of cerebral infarction.

The cerebral infarct consists of a central area of necrosis or softening, surrounded by an area of vasodilatation, edema and punctate hemorrhage. This vasoparalysis and edema is not unknown in peripheral vascular occlusions. In a muscle infarct of the anterior tibial muscle, the entire compartment becomes maximally swollen and the edematous muscle herniates through the incised fascia. In the closed cavity of the skull, cerebral edema is far more apt to interfere with circulation and gas exchange in the terminal vascular bed. The soft brain tissue gives no elastic support to the arterial wall, and cerebral softening damages the terminal vascular bed.

When Kety and his co-workers described their nitrous oxide method for the determination of cerebral blood flow and cerebral vascular resistance, it was felt by many that their failure to demonstrate an increase in blood flow after vasoconstrictor paralysis pointed to the futility of blocks for apoplexy. A brief consideration of their method, however, would indicate that this conclusion, which the authors themselves never expressed, is a fallacy.

Cerebral vascular resistance is determined by dividing the prevailing mean blood pressure by the calculated blood flow per 100 gm. of brain per minute. This figure represents the number of millimeters of mercury of mean arterial pressure required to drive 1 c.c. of blood through 100 gm. of brain in one minute. The method, however, assumes that the mean blood pressure in the femoral artery is identical with that in the *internal carotid artery after block*. It seems likely that the blood pressure in the internal carotid artery falls after block, because we have good evidence that sympathetic block relaxes the arterial wall and that intra-arterial pressure falls. Furthermore, one would like to see cerebrovascular resistance calculated in cerebral infarcts, since it may well be high. It is known that sympathectomy decreases collateral resistance.[15] My co-workers and I have previously emphasized [16] that the concept of *spasm* is unnecessary in establishing the need for sympathectomy, and that removal of vascular resistance, mainly from the collateral bed, is what vasomotor paralysis accomplishes.

One is tempted to propose, then—and this is confirmed by the blood flow studies of Shenkin following bilateral stellectomy [10]—that cerebral vascular resistance is decreased after blocking of vasoconstrictors, and this must certainly be of benefit to an ischemic cerebral area.

The effect of unilateral carotid artery ligation is a marked increase in cerebrovascular resistance.[17] This resistance develops as a result of the flow through the circle of Willis, and its sclerosis or its anomalous configuration may well be a decisive factor for the presence or absence of an effective collateral circulation (figure 3).

The collateral circulation in the brain is variably developed. Under normal conditions the blood of the two internal carotid arteries does not mix. Only when a vascular block occurs will the communicating arteries of the circle of Willis come into play. The anomalies of the circle of Willis have a decisive influence on the development of cerebral softening and hemorrhage.[18]

Other considerations are relevant. One is the emphasis of Corday, Rottenberg and Putnam [19] on cerebral vascular insufficiency in analogy with coronary insufficiency. They obtained experimental and clinical evidence that, in the presence of a narrowed, sclerotic cerebral vascular bed, systemic hypotension of any kind may bring on electroencephalographic changes, hemiplegia or hemianesthesia, all of which may be transient if the blood pressure is promptly restored. They do not emphasize, however, that dur-

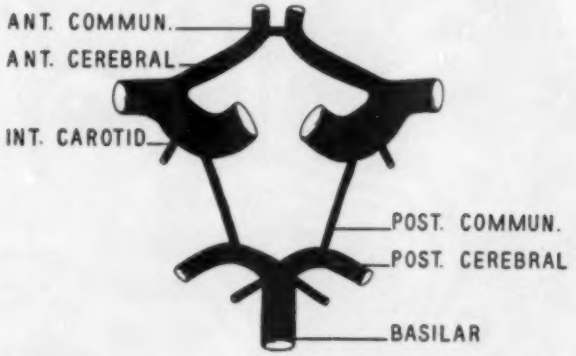

FIG. 3. The average pattern of the circle of Willis. This pattern was present in only about 50% of cadavers examined by Fetterman and Moran (Arch. Path. 32: 251, 1941).

ing the hypotensive period the cerebral vessels may readily attain their critical closing pressure,[20] a figure which may be lowered by sympathetic paralysis, as shown by Burton.[21]

Thus, while the concept of cerebral vascular insufficiency is most helpful in explaining transient hemiplegia without the presence of vasospasm, it by no means indicates that regional vasoconstrictor paralysis would be useless in such a situation.

The syndrome of cerebral venous thrombosis following childbirth is another entity,[22] of which we have seen one case. A block was not done here because of rapid spontaneous improvement. Finally, thrombosis of the internal carotid artery has become a recognized clinical entity with three clinical patterns: catastrophic onset, slowly progressive course and transient attacks of paralysis. Johnson and Walker collected 107 such cases, including six of their own.[23]

Clinical Observations

When the patient arrives at the hospital his blood pressure at entrance may be *lower or higher than at the time of the accident.* The blood pressure recorded in his hospital chart may represent a state of cardiac or

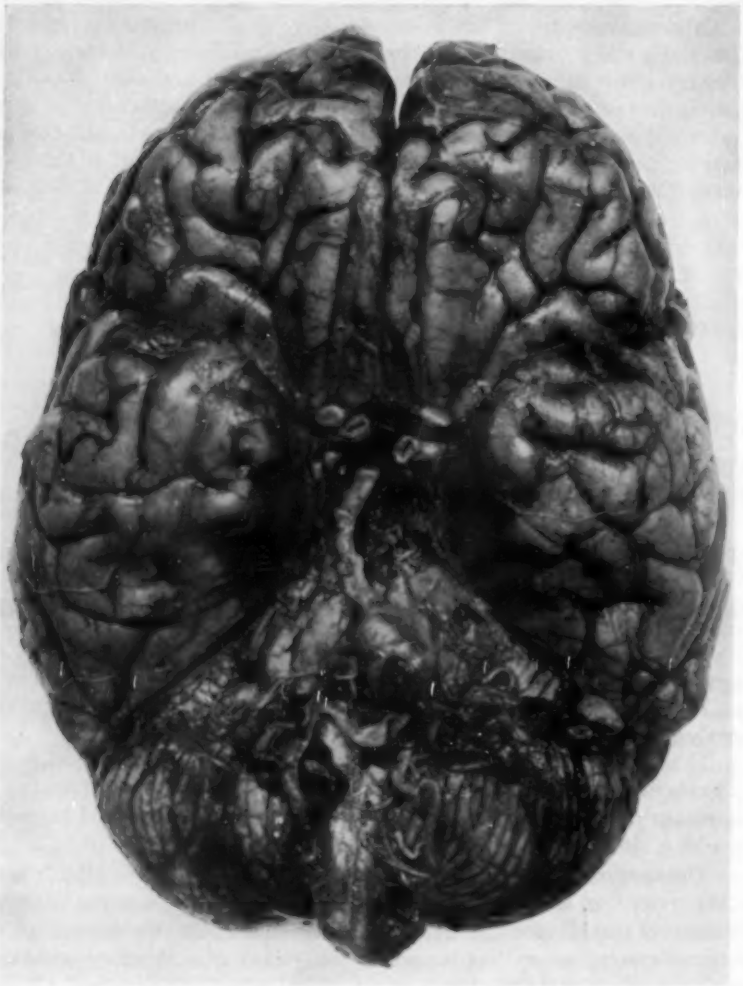

Fig. 4. Saccular aneurysm of the basilar artery, with large subdural hemorrhage, old myocardial infarct and bilateral popliteal aneurysms. Onset here was slow; weakness and tingling with increasing drowsiness preceded the final coma for weeks. St. Luke's Autopsy 278, 1948.

peripheral failure or a reactive pressor response to increased intracranial pressure.[1] The presence of an obvious thrombotic cardiac lesion or the history of previous peripheral emboli, together with normal blood pressures, normal spinal fluid pressure and absence of bloody spinal fluid, has called for a cervical sympathetic block, and the results in this group have been encouraging. Of the 25 patients we reported in 1948, and the additional 79 patients which Gilbert and I reported in a letter to the Editor of the *Journal of the American Medical Association*,[24] there was a total of *14 emboli*. Two of these patients died later, but every one showed *an immediate favorable response* which will be defined shortly.

The present additional series of 80 patients contained a group who were either treated at home or in whom insufficient data were obtained. This left us with 54 on whom accurate data are available. Twenty of these gave clear-cut evidence of massive hemorrhage, three were diagnosed as brain tumor, and one as a subarachnoid hemorrhage with the postmortem finding of an aneurysm of the basilar artery (figure 4). This leaves 30 patients who were regarded as having thrombotic occlusions, but on the basis of what has been said in the previous paragraphs one would rather classify these as cerebral infarcts, with more or less hemorrhage in and around the infarct.

We do not have many second spinal punctures, but patients whose spinal fluid was bloody or frankly xanthochromic four to five days after the insult have been regarded as having hemorrhagic infarcts. Of the 30 patients, 10 obtained no relief, nine obtained dubious relief, and in 11 the relief was definite.

Causes of Failure

Probably the most potent reason for a slow acceptance of this method is the large percentage of failures. In figure 5 I have summarized the available data from the literature, including our own. As causes of failure the following factors emerge:

1. Spreading intracerebral hemorrhage and edema.
2. Intraventricular hemorrhage.
3. Time factor (patients injected more than 24 hours after the cerebral vascular accident).
4. Severe vascular sclerosis, including coronary sclerosis with prolonged hypotension.
5. Shocklike state and loss of consciousness.
6. The state of the circle of Willis.

Personal Material Studied

To date, 55 patients suffering from apoplexy have been injected once or several times. This includes 25 patients discussed in our first report in

TABLE 1

Number of Injections Received by Apoplectic Patients

Number of Patients	Number of Injections
30	One (30)
10	Two (20)
9	Three (27)
4	Five (20)
2	Six (12)
55	109

Two patients had an indwelling plastic catheter for 5 to 7 days, respectively; five patients received bilateral sympathetic blocks.

1948,[1] together with an additional 80 patients observed since that time, of whom only 30 were selected for analysis, the rest either being injected at home or lacking important data. Twenty patients had frankly bloody spinal fluid and were not injected, three were diagnosed as having a brain tumor, and one had a subarachnoid hemorrhage.

The 55 patients received from one to 10 injections daily. Table 1 indicates the number of injections given during the course of treatment. Forty-eight patients received 90 sympathetic blocks. In addition, plastic catheters were left in the vicinity of the cervical sympathetic chain in two

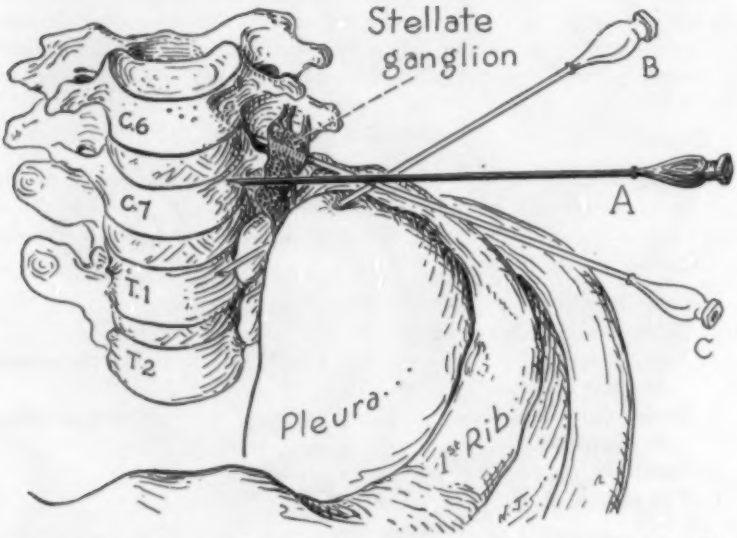

FIG. 5. Injection of cervical sympathetic trunk by a lateral approach. A. Correct position of the needle, at right angles to the spinal column. B. The needle has been directed caudally for the search for the first rib, which is unnecessary; puncture of the pleura or lung may result. C. The needle has been directed cephalad and may pierce the dural covering of the root or enter the intervertebral foramen and puncture the cord. From Gilbert and deTakats.[1]

patients for five and seven days, respectively. Lately we have carried out bilateral injections in five patients.

Injections were given only once if there was complete regression of neurologic symptoms or if the result was completely negative in spite of the appearance of a Horner's syndrome. Horner's syndrome did not occur in three out of 22 patients, an incidence of 14%. The standing order was to repeat the block if Horner's syndrome did not develop, but this was not always carried out. Injections were continued daily if improvement was noted but did not persist.

TABLE 2

Sympathetic Block in Apoplexy

A. Injected

Diagnosis	No. of Cases	Improvement	Failure
Embolus	14	14	—
Infarct	41	18	23
Total injected	55	32	23

B. Not Injected

Massive hemorrhage	23
Subarachnoid hemorrhage	1
Cerebral venous thrombosis	1
Brain tumor	3

Technic: The technic of injection has been illustrated before and is shown again (figure 5). It is followed by no untoward results especially if the needle is directed to the sixth instead of the seventh transverse process. Some residents prefer a more direct approach next to the trachea, but our method seems easier for the occasional operator. It is important, however, that if a Horner's syndrome does not appear in 10 to 15 minutes a re-injection be done.

TABLE 3

Improvement Following Cervical Sympathetic Block

55 Patients

	Patients	Per cent
Consciousness regained	10	17
Speech regained	7	12
Speech improved	15	27
Motor improvement	12	21
Flaccid paralysis abolished	8	14
No improvement	23	41

Untoward Results: In our early experience, pneumothorax or lung collapse occurred when patients were injected for causalgic states. In one case observed at a Veterans Hospital during World War II, the needle punctured the cord through the intervertebral foramen and caused the patient's death. We have not, however, encountered any mishaps with this method in the last six years, although all residents on the vascular surgical service, to-

gether with medical and anesthesia residents, performed well over 200 cervical sympathetic blocks.

Failure of the Block: I have already discussed the causes of failures. In our personal series there were none in the embolic group and 55% in the group classified as "infarct." That this "infarct" may mask a hemorrhage or a venous thrombosis, or be caused by a cerebral vascular insufficiency, has already been mentioned. At present, however, a more exact diagnosis of apoplexies does not seem possible, and from 10 to 15 patients may be treated consecutively without any improvement.

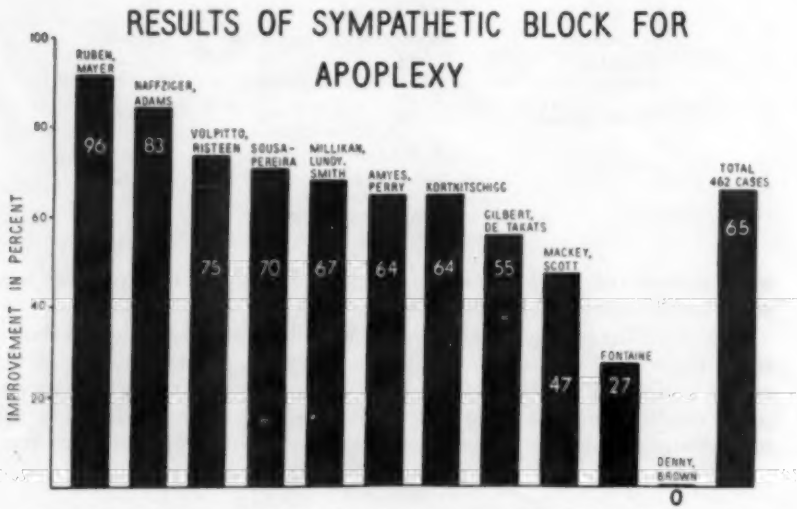

FIG. 6. Note the great variability of response to sympathetic block; 96% improvement in the cases of Ruben and Mayer, to no improvement in Denny-Brown's observations. The first two cases of Leriche, both successful, are not included. Of a total of 462 patients, 302 (65%) were reported as obtaining benefit. Our own series shows a somewhat lower percentage of improvement.

Definite Results: Among the 56 patients, all 14 diagnosed as cerebral embolism improved, provided the injection was done within the first six hours (table 2). Of the infarcts, 19 of 41 patients showed improvement, and the type of improvement is shown in table 3. Excluded from the injection were 28 cases of apoplexy in this series suffering from intracerebral or subarachnoid hemorrhage, venous thrombosis or brain tumor.

SUMMARY OF RESULTS FROM THE LITERATURE (FIGURE 6)

With no claim to a complete review of all the cases of apoplexy reported to have been treated by sympathetic block, a table has been prepared in

which the number of cases with the improvement and failure of the procedure have been listed. Among the 462 cases, 302 (65%) have been reported as obtaining benefit, whereas 160 (35%) were failures. "Good" results were listed with the improvements, whereas "dubious" results were listed with the failures. The 65% improvement is higher than that we observed in our own series (i.e., 55%) and is predominantly due to the enthusiastic report of Naffziger and Adams, who noted 128 patients with improvement among 155 treated. That all 10 authors listed in this table were victims of an infectious epidemic of credulity and self-deception, as a distinguished neurologist recently expressed himself,[25] is difficult to believe.

Discussion

The large percentage of failures with this method would indicate one of two possibilities: either the sympathetic blocks have no value,[26] or we are unable to recognize clinically certain patients in whom the block cannot be effective. Because of the clear-cut rapid improvement in some instances, I am inclined to believe that our clinical diagnosis of vascular accidents in the brain is inadequate. The presence of cerebral hemorrhage, the extent of cerebrovascular sclerosis which will not respond even to the most potent vasodilator, CO_2, and the pattern of the circle of Willis, which is incomplete in 50% of all individuals, are factors which are mostly unknown at the emergency admission of the apoplectic patient. Cerebral angiography is not practiced in apoplexies generally, and its proper use requires neurosurgical judgment.

Obviously, sympathetic block can help only if the infarct is surrounded by a zone of edema and vasoparalysis, if the cerebral vessels are not unduly sclerotic, and if the circle of Willis is able to function as an effective shunt when one internal carotid artery or its main branches are blocked. Also, if prolonged hypotension exists a temporary revascularization of the ischemic infarct by sympathetic paralysis cannot take place.

Since these factors are unknown and since the method is simple and harmless, one cannot deprive an apoplectic unconscious patient of a possible benefit. Our group has never claimed that residual damage or mortality is decreased by such a procedure. However, since the slow phase of restitution, taking several weeks or months, has been accelerated in 19 out of 41 patients thought to have cerebral infarcts, we intend to continue its use on selected patients.

The mechanism of the observed improvement has eluded us. Relief of vasospasm is an obvious answer, but one has no proof of vasospasm, and our best results with sympathectomy are in peripheral arteriosclerosis of the extremities exhibiting no vasospasm. Decrease in cerebral vascular resistance is measurable after stellate ganglionectomy, and it is also known that any collateral circulation thrown into action following vascular occlusion creates an increased vascular resistance. Since collateral circulation

may be activated not only from the branches of the affected internal carotid artery but also from the opposite side and possibly through anastomosis with the external carotid artery (figure 7),[27] a bilateral cervical sympathetic block done half an hour apart seems worth considering.

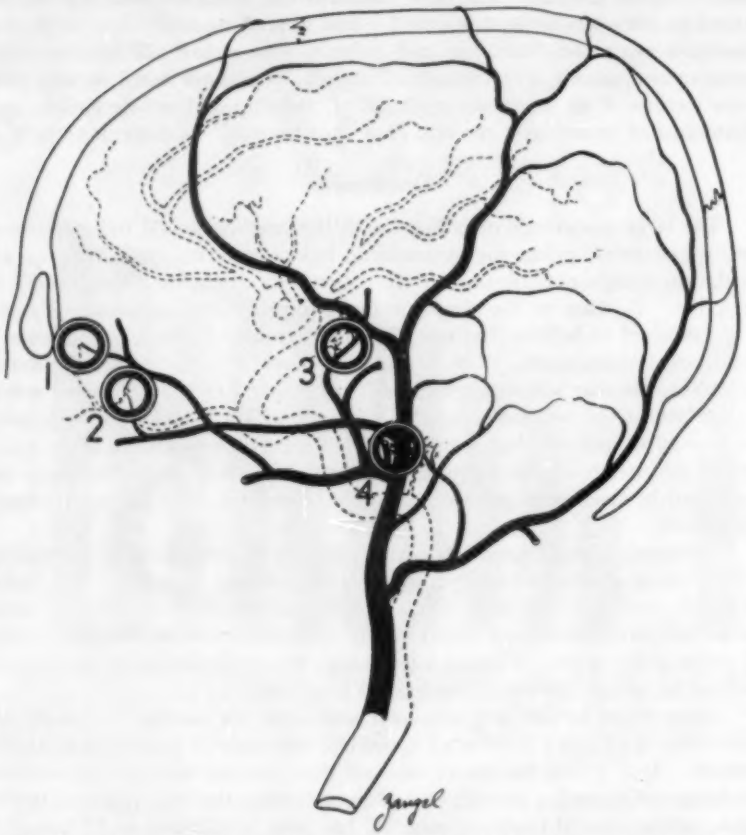

FIG. 7. Anastomoses between the external and internal carotid arteries. Branches of the external carotid through the angular, supraorbital, lacrimal and nasociliary arteries connect with branches of the ophthalmic. In chronic arterial occlusion there is angiographic evidence that such anastomoses function:[27] (1) anterior meningeal with posterior meningeal; (2) ophthalmic with interior and exterior maxillary; (3) lacrimal and nasociliary with internal maxillary and occipital; (4) caroticotympanic with internal maxillary arteries.

Other as yet unexplored mechanisms—such as the effect of strong sensory stimulation on a refractory state of the brain, the activation of vasodilator fibers, the effect of procaine itself deposited in paravertebral tissue—may have to be thought of. As has often been the case in the past, clinical

observations antedate the demonstration of the modus operandi of a useful procedure.

Summary

The arguments for and against the use of cervical sympathetic block in apoplexy have been discussed. It would seem from the study of the literature and from personal observations on 55 patients so treated that there is at present no way of selecting the suitable case, and that only half of the patients derive definite benefit from the procedure. However, the technic advocated is harmless, and the results when obtained are so gratifying that further study and use of this method seem indicated.

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A CLINICAL EVALUATION OF ORAL VERILOID IN THE TREATMENT OF HYPERTENSIVE DISEASE*

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THE focus of attention in the treatment of hypertensive disease has turned toward the use of hypotensive drugs. Among a number of hypotensive drugs which have stimulated interest are preparations of *Veratrum viride* and its derivatives. *V. viride* is not new to pharmacologic or clinical experience. A rebirth of interest in this drug followed more accurate standardization and better knowledge of its composition and actions.[4, 10, 5]

An oral preparation of Veriloid is evaluated in this study. Veriloid is a standardized mixture of hypotensive alkaloids of *V. viride* [20] whose main pharmacologic actions produce hypotension, bradycardia and emesis. The chemical structure and relative potencies of the alkaloids of Veriloid have been described.[4, 12] The hypotensive effect of Veriloid is believed to be mediated by a direct action on the medullary vasomotor center [17, 19] and the carotid sinus.[17] Bradycardia is mediated by afferent vagal fibers distributed to the vagal inhibitory center.[10, 17, 19] It has been suggested from animal experiments that the emetic effects result from central action near the nodose ganglion in the brain stem, rather than from local gastrointestinal irritation.[8, 2]

PURPOSE

A review of the reports on the effects of Veriloid in the treatment of hypertensive disease indicated the need for a controlled study on a group of hospitalized patients kept under careful observation. In view of the many unsatisfactory therapeutic results obtained in other clinical studies employing Veriloid, the question arose as to whether the doses used were large enough to provide a therapeutic effect. The average of the daily doses of Veriloid employed in the clinical studies reviewed was about 17 mg. A daily dose of 30 mg. or more was rarely used.[9, 11, 15, 24] The dosage levels of Veriloid employed in this study were considerably higher than those previously reported, and the group of patients selected appeared more severely disabled by their disease.

Thirteen hospitalized male patients were studied. Their average age was 45, and the average duration of hypertension was 8.6 years. Only one patient was subsequently autopsied, but the most probable subdivision by clinical diagnoses was: five patients with essential hypertension, one with chronic glomerulonephritis, and seven with malignant hypertension. Of

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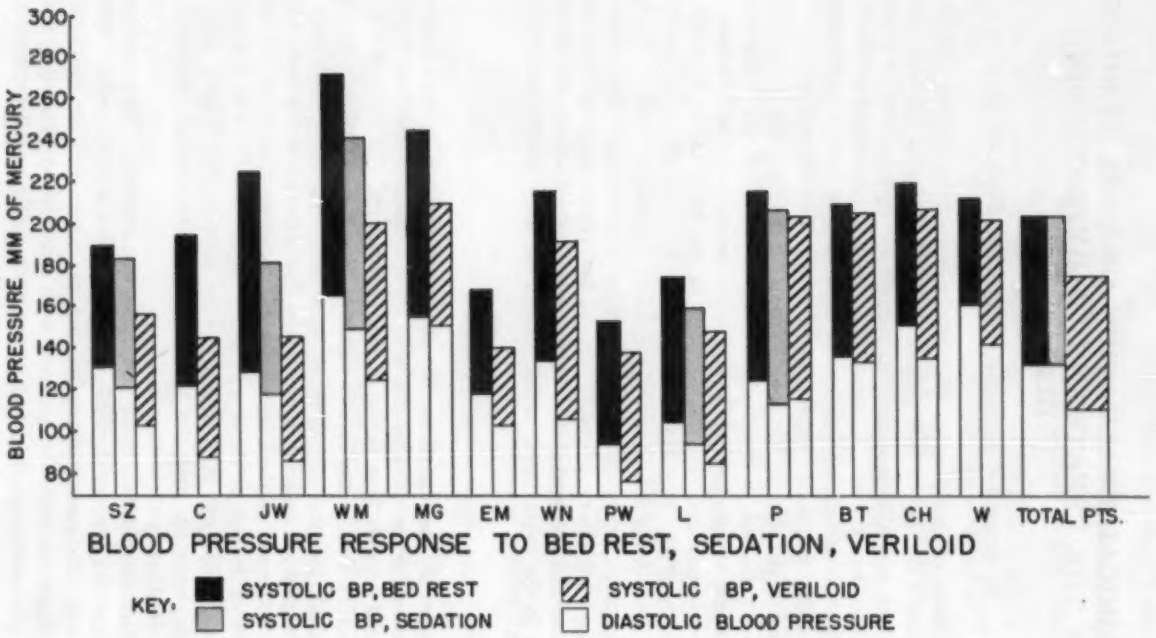
BLOOD PRESSURE MM OF MERCURY
300
280
260
240
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200
180
160
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120
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TOTAL PTS.
BLOOD PRESSURE RESPONSE TO BED REST, SEDATION, VERILOID
KEY:
SYSTOLIC BP, BED REST
SYSTOLIC BP, SEDATION
SYSTOLIC BP, VERILOID
DIASTOLIC BLOOD PRESSURE

FIG. 1.

the malignant hypertensives, five had malignant essential hypertension, one had chronic glomerulonephritis, and one had chronic pyelonephritis.

Eleven patients had cardiac involvement, and five gave a recent history of congestive failure. Eleven had significant renal involvement. All 13 had retinopathy, seven had Grade IV retinopathy, three had Grade III retinopathy, and three had Grade I–II retinopathy. Five gave a history of cerebrovascular disturbance.

Of the initial complaints, nine had significant headache, six complained of dizziness, four had blurring of vision, four had varying degrees of dyspnea and three had emotional instability.

Methods

In order to evaluate the effectiveness of Veriloid in the treatment of hypertension, its effects on blood pressure, pulse pressure, heart rate and size, electrocardiographic patterns, retinopathy, renal function, cerebrovascular disturbances, congestive heart failure and subjective complaints were all closely observed.

Control periods varied from six days to four weeks. The average control period was two weeks. In most instances determinations of blood pressure and heart rate were made at 10 a.m. and 6 p.m. daily. These were averaged to give the control blood pressures and heart rates. Benzodioxane tests, funduscopic examination, chest x-rays, cardiac fluoroscopy and electrocardiograms were performed routinely during the control period. Renal function was evaluated by urinalysis, blood urea nitrogen, urine concentration test, phenolsulfonphthalein excretion, urea clearance and intravenous pyelography. When indicated, retrograde pyelography was performed, and in each case other laboratory data were obtained sufficient to establish a diagnosis and determine suitable treatment.

These studies were repeated several times while the patient was receiving Veriloid. Blood pressure determinations were made at the time the patient received Veriloid, and one hour afterward. The 10 a.m. and 6 p.m. blood pressure determinations were used in compiling data. They were often not the lowest blood pressures observed during the day but were considered to be most representative.

One or 2 mg. tablets of Veriloid were employed, and patients initially received 3 mg. four times a day after meals. This was increased by increments of 2 to 4 mg. a day until a hypotensive or emetic response occurred. Often these came almost simultaneously, but fortunately in some instances the hypotensive effect appeared first. Once a hypotensive effect was achieved, considerable readjustment of the dosage schedule was necessary to maintain a sustained hypotensive response. On continuous administration the hypotensive effect usually appeared one-half to one hour after a dose. The effect appeared to be dissipated within four to five hours. The hypo-

tensive response was not smooth in the sense that onset of action and peak of effect were almost simultaneous.

Results

1. *Blood Pressure:* Eleven of 13 patients had a reduction in their blood pressures below control levels. The results are summarized in figure 1.

If a reduction in blood pressure of 25 mm. of mercury systolic and 15 mm. diastolic is selected as being significant, eight patients had significant reduction of systolic and 10 patients had significant reduction of diastolic blood pressure. Seven patients had significant reduction of both their systolic and diastolic blood pressure. In three patients normotensive levels were obtained in a stable manner on prolonged drug administration. Five other patients had several transitory sharp reductions in blood pressure to normotensive levels. Four patients had a hypotensive response greater than 40/30 mm. of Hg, and two of these patients had average reductions of 76/33 and 70/40 mm. of Hg.

The average control blood pressure of all 13 patients was 208/135 mm. of Hg. The average of all blood pressures during Veriloid administration was 179/114 mm. of Hg. The average reduction in blood pressure was 29/21 mm. of Hg.

The comparison of the results obtained in the different types of hypertension in this group is summarized in figure 2.

Of five patients with essential nonmalignant hypertension, four had a significant reduction in diastolic blood pressure, and three also had a significant systolic reduction. The single patient with nonmalignant renal hypertension had a significant reduction of both systolic and diastolic blood pressure.

Five of seven patients with malignant hypertension had significant reductions of diastolic blood pressure, and three also had a significant systolic reduction. Five of six patients with nonmalignant hypertension had significant reductions of diastolic blood pressure; and four also had a significant systolic reduction. Seven of nine patients with essential hypertension of the malignant and nonmalignant varieties had significant reductions of diastolic blood pressure, and five also had a significant systolic reduction. Three of four patients with hypertension secondary to renal disease had significant diastolic reductions, and two also had significant systolic reduction. It would appear that Veriloid is about equally effective in the treatment of all the forms of hypertension encountered in this study.

The effectiveness of Veriloid in reducing blood pressure appears to be inversely proportional to the duration of hypertension. The results are summarized in figure 3.

Of four patients in whom the duration of hypertension was three years or less, all had significant reductions of both systolic and diastolic blood pressure. Six of nine patients whose hypertension had lasted more than

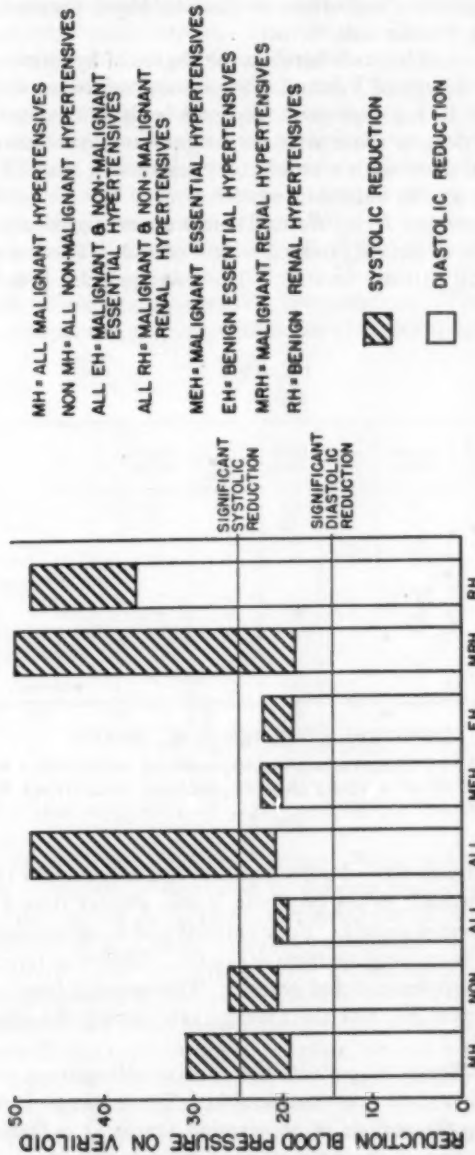
MH = ALL MALIGNANT HYPERTENSIVES
NON MH = ALL NON-MALIGNANT HYPERTENSIVES
ALL EH = MALIGNANT & NON-MALIGNANT ESSENTIAL HYPERTENSIVES
ALL RH = MALIGNANT & NON-MALIGNANT RENAL HYPERTENSIVES
MEH = MALIGNANT ESSENTIAL HYPERTENSIVES
EH = BENIGN ESSENTIAL HYPERTENSIVES
MRH = MALIGNANT RENAL HYPERTENSIVES
RH = BENIGN RENAL HYPERTENSIVES
SIGNIFICANT SYSTOLIC REDUCTION
SIGNIFICANT DIASTOLIC REDUCTION
SYSTOLIC REDUCTION
DIASTOLIC REDUCTION
REDUCTION BLOOD PRESSURE ON VERILOID
0
10
20
30
40
50
MH
NON MH
ALL EH
ALL RH
MEH
EH
MRH
RH
TYPES OF HYPERTENSIVE DISEASE

Fig. 2.

three years had significant reductions of diastolic blood pressure, and three also had significant systolic reductions.

No correlation could be made between the degree of hypotensive response and the size of the dosage of Veriloid. Significant responses were obtained with daily doses of 10 mg. and poor responses with daily doses of 40 mg. The average daily dose in those with an insignificant hypotensive response was 29 mg., and in those with a satisfactory response it was 32 mg. Sensitivity to Veriloid was an individual matter.

2. *Pulse Pressure and Heart Rate:* There were no significant alterations in the pulse pressure of patients treated with Veriloid. The average control pulse pressure of all patients was 66. The average pulse pressure during

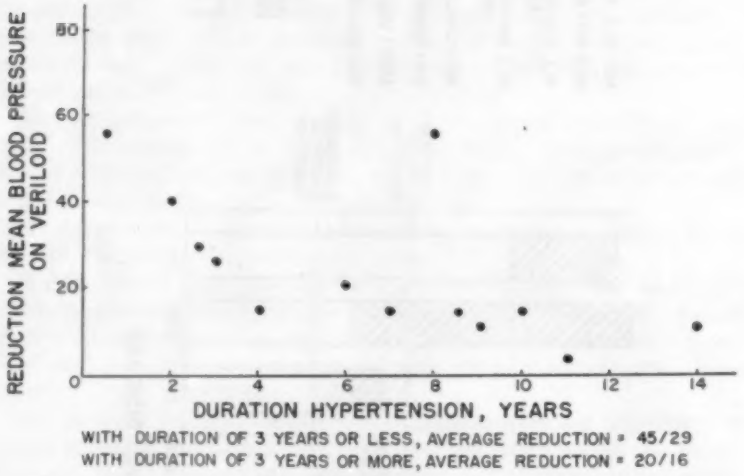

FIG. 3.

the Veriloid period was 61. Twelve patients had a reduction of heart rate while receiving Veriloid; in six of whom it was greater than 15 beats per minute over a prolonged period. Four patients had acute episodes of bradycardia, with heart rates ranging from 40 to 60. This was frequently associated with acute hypotension and emesis. The average heart rate during the control period was 84, and the average rate during the administration of Veriloid was 72.

3. *Heart Size:* Ten of 12 patients had cardiac enlargement on admission to the hospital, and in six it was considerable. There was no further cardiac enlargement during the periods of observation (table 1). During Veriloid administration the size of the heart of nine patients decreased, but in only one was the reduction of any considerable degree.

4. *Electrocardiographic Changes:* Eleven of 12 patients had patterns showing left ventricular strain. During the control period 10 patients showed no change in their electrocardiograms (table 1). A single patient had minor T wave changes toward normal. During Veriloid therapy the electrocardiogram remained unchanged in seven. In a single patient with left ventricular strain, reversion to a normal electrocardiogram was demonstrable on Veriloid administration, and minor T wave changes toward normal were demonstrated in three others. In those patients with some electrocardiographic improvement the control blood pressures, the reductions of blood pressure with Veriloid, and the daily doses of Veriloid were averaged as a group and were found to be almost identical to the results in those patients with no electrocardiographic improvement. The average duration of hypertension in the patients with some electrocardiographic response to

TABLE 1
Results

	Hypertension	Cardiac Enlargement	EKG LVS	CHF	Retinopathy	Renal Function	Cerebrovascular	Subjective
Number evaluated	13	12	12	13	13	13	13	13
Number involved	13	10	11	5	13	11	4	11
Unchanged control	6	9	10	1	10	11	1	6
Improved control	5	1	1	3	1	0	0	2
Significant improvement control	1	0	0	3	1	0	0	0
Worse control	2	0	0	1	2	0	3	3
Improved Veriloid	12	9	4	1	4	1	4	10
Significant improvement Veriloid	7	1	1	1	4	0	2	4
Unresponsive Veriloid	1	0	7	1	9	10	0	1
Worse Veriloid	0	0	0	0	0	0	0	0

LVS—Left Ventricular Strain
CHF—Congestive Heart Failure

Veriloid was four and one-half years, and in the unresponsive it was 10 years.

5. *Congestive Heart Failure:* Wilkins, Freis and Stanton [28] reported that cardiac output never decreased in patients treated with Vertavis, but increased in two patients who had been treated for left ventricular failure.

Five patients in this study entered the hospital in varying degrees of congestive failure (table 1). Three were treated by other means and were no longer in congestive failure when Veriloid therapy was instituted. One of these patients had considerable further reduction in size of the heart during Veriloid therapy. A fourth patient, treated by other means, was considered to be mildly decompensated when Veriloid was instituted. There was no further change in his clinical state during Veriloid therapy.

A fifth patient with hypertensive heart disease entered the hospital in marked left- and right-sided congestive failure. On digitalis, bed-rest, salt restriction and mercurial therapy he remained in the category of intractable

heart failure for a period of four weeks. One week after the commencement of Veriloid therapy the liver diminished in size and the heart size decreased. There was clearing of râles in two weeks. Veriloid was discontinued because of severe emesis, and six days later the patient was again in marked failure. With re-institution of Veriloid the failure again cleared. It would appear that Veriloid may have an adjuvant rôle in the treatment of certain instances of hypertensive cardiac failure.

6. *Retinopathy:* It has been stated that there is a reduction in the peripheral resistance of retinal arterioles in veratrum-treated hypertensives.[6, 22] In this study all patients had retinopathy. The results are summarized in table 2.

Of seven patients with Grade IV retinopathy (papilledema), five were unchanged during the control period, and two had increasing papilledema, hemorrhages and exudates. Six of the seven patients with papilledema were adequately followed during Veriloid therapy. Papilledema disappeared

TABLE 2

Response of Retinopathy to Veriloid Therapy

Degree of Retinopathy	Grade IV	Grade III	Grade I–II
Classification control	7	3	3
Unchanged control	5	2	3
Improved control	0	1	0
Worse control	2	0	0
Adequately followed Veriloid period	6	3	3
Improved Veriloid	3	1	0
Unchanged Veriloid	3	1	3
Worse Veriloid	0	0	0
Final classification on Veriloid	3	4	5

in three (who were reclassified as having Grade III retinopathy), and three were unchanged. Of the three patients who originally had Grade III retinopathy, one improved to Grade I–II retinopathy during the control period. Two patients continued to have Grade III retinopathy when Veriloid was instituted, one remained unchanged, and one improved to Grade I–II retinopathy on Veriloid. There were no changes in the three patients originally in Grade I–II during the control or Veriloid periods. The over-all result of Veriloid therapy was no change in about two thirds, and improvement in one third.

There was no correlation between duration of hypertension and the existence of Grade IV retinopathy. There was a considerable correlation between the degree of hypertension and the severity of retinopathy. The patients with Grade IV had an average control blood pressure of 229/150 mm. of Hg. The patients with Grade III had an average of 200/127 mm. of Hg, and the patients with Grade I–II had an average of 167/107 mm.

of Hg. There was no direct relationship between the dosage of Veriloid or the magnitude of the hypotensive response and improvement of the retinopathy.

7. *Renal Function:* Goldman and Frierson,[7] using Veriloid intravenously in hypertensive patients, showed that the usual renal hemodynamic responses were a moderate reduction in glomerular filtration, a slight rise in renal plasma flow and a fall in filtration fraction. The results of the clinical findings of this study are summarized in table 3. The 15 minute phenolsulfonphthalein excretion during Veriloid therapy showed rather marked improvement in two patients and moderate improvement in two others. This improvement was not paralleled by other renal studies, and its significance is not clear. There were no significant changes in urine concentration, urea clearance or microscopic urinary findings. There were no significant changes in blood urea nitrogen that were not explainable by progression of the disease (one patient), or transient prerenal azotemia resulting from Veriloid-induced emesis (one patient). Veriloid does not appear to improve or depress renal function in hypertensive patients as measured by these technics.

TABLE 3

Effect of Veriloid on Clinical Renal Function Studies

	Significantly Improved	Essentially Unchanged
Blood urea nitrogen	0	11
Albuminuria	1	10
Phenolsulfonphthalein	4	7
Urea clearance	1	10
Urine concentration	0	11
Microscopic changes	0	11

8. *Cerebrovascular Effects:* Moyer and associates [16] measured the cerebral hemodynamics of a group of patients with hypertensive encephalopathy treated with Veriloid intravenously. They found that cerebrovascular dilatation and fall in cerebral peripheral resistance accompanied the fall in systemic blood pressure, resulting in a maintenance of normal cerebral blood flow and oxygen uptake.

Five patients in this study gave a history of cerebrovascular disturbance. In four the disturbance was of recent occurrence (table 1). One patient with hypertensive encephalopathy had severe headaches, marked blurring of vision (nearly to the point of blindness), and syncopal episodes followed by paresthesia. Physical examination suggested an old left hemiparesis. During the control period he was semistuporous, and his other severe symptoms were unmitigated. It is difficult to measure cerebrovascular functional improvement objectively, but his subjective improvement was impressive. Following the first full day of Veriloid therapy the patient was greatly improved and completely alert. He was able to leave his bed and walk about, his headaches were gone, and his vision was now clear. During several

weeks of observation the patient did not have a single headache, his vision remained clear, and syncope did not reappear. A second patient had a cerebrovascular accident with left hemiparesis eight weeks prior to admission, with recurrence of a more transient episode 10 days prior to admission. After seven weeks of hospitalization here on a rice diet he had a convulsive seizure and another transient left hemiparesis. He also frequently complained of left-sided paresthesia. During 12 weeks of observation while treated with Veriloid there was no recurrence of cerebrovascular disturbance, and paresthesia was considerably reduced.

A third patient developed a transient right hemiparesis shortly after discontinuance of Veriloid, but he remained free of cerebrovascular disturbance when Veriloid was re-instituted. A fourth patient died of a cerebrovascular accident, with a marked rise in blood pressure to 260/190 mm. of Hg after Veriloid and antihypertensive agents were discontinued. A word of caution must be given in interpreting the changes that occurred in the last two patients described. There was no provable relationship between

TABLE 4

Subjective Response of Chief Complaints to Veriloid Therapy

	Marked Improvement	Moderate Improvement	Essentially Unchanged	Worse	Total
Headache	5	3	1	0	9
Blurring of vision	1	0	3	0	4
Dizziness and weakness	3	2	1	0	6
Nervousness	0	1	2	0	3
Other neurologic symptoms	0	1	0	0	1
Sense of well being	3	2	2	0	7

discontinuance of Veriloid and occurrence of cerebrovascular disturbance. None of the 13 patients developed cerebrovascular disturbances while they were receiving Veriloid.

9. *Subjective Effects:* The influence of Veriloid on the significant initial complaints is evaluated in table 4. This is an evaluation of the effect on individual symptoms, but if one considers all subjective changes together in each patient, it can be said that 60% of the patients were markedly or moderately improved by the use of Veriloid, and another 30% were slightly improved.

10. *Dosage of Veriloid:* The doses of Veriloid employed in this study were considerably higher than those in other published clinical investigations. The highest daily dose in any patient was 84 mg. This was maintained for several weeks, but the patient eventually developed troublesome gastrointestinal disturbances and his daily dose was reduced to 64 mg. The average of maximal tolerated therapeutic doses for all 13 patients was 39 mg. a day. Eight patients were able to tolerate a maximal dose for varying periods, but later had to have their dose readjusted to lower levels. The

average of final doses for all patients was 32 mg. a day. The readjusted dose levels seemed to produce no less of a hypotensive effect than the original tolerated doses.

11. *Toxic Effects:* The symptoms of nausea, emesis and anorexia which occur on administration of Veriloid result from a physiologic action of the drug.

The frequency and severity of gastrointestinal symptoms induced by Veriloid were impressive. One hundred per cent of the patients had nausea and emesis, and in 77% these symptoms were of considerable severity. The therapeutic index was small in all patients. In two patients the emetic effect appeared before any hypotensive response was achieved. In two other patients satisfactory hypotensive responses and major emetic effects appeared simultaneously. In these four patients (31% of the group), Veriloid had to be permanently discontinued. Six other patients had marked emetic effects, and in these patients doses were readjusted to lower levels. Even at minimal therapeutic levels, three of these six continued to have occasional gastrointestinal symptoms. The three other patients in the study had only mild emetic effects.

Nausea and emesis usually occurred one or two hours after a dose of Veriloid, and in some patients it was accompanied by acute hypotension and bradycardia. In most instances the emetic episodes occurred suddenly and explosively, with no forewarning. Relief after emesis appeared promptly, without continuance of lingering symptoms. Prolonged anorexia without emesis was infrequent and was of significance in only one patient. Emesis was considerably reduced when Veriloid was given about one hour after meals rather than at meal times. The emetic threshold was an individual matter, and there was no overall relationship between the size of the dose and the severity of gastrointestinal symptoms.

Excessive salivation and epigastric burning were present in a few patients but were less prominent than in other studies. There were no instances of peripheral vascular collapse, respiratory depression, allergic manifestations or other toxic phenomena. Acute hypotension and bradycardia were of temporary duration and were never threatening.

Conclusions

Viewed primarily as a hypotensive agent, Veriloid demonstrated considerable ability to lower blood pressure. It appeared to be equally effective in malignant and nonmalignant hypertension, and in hypertension of renal origin as well as in essential hypertension. Veriloid was less effective with increasing duration of hypertension. There were suggestions that Veriloid may have an adjuvant rôle in the treatment of congestive failure of hypertensive heart disease, and that it produces beneficial results in hypertensive cerebrovascular disturbances. In some patients there was reduction in cardiac enlargement and in retinopathy, and improvement in abnormal elec-

trocardiographic patterns. Veriloid did not appear to have any harmful cardiac, cerebrovascular or other vascular effects. It did not appear to influence other physiologic mechanisms adversely. As used here on hospitalized patients under careful supervision, Veriloid does not appear to be a dangerous drug.

When consideration is given to the severity of the disease in this group of patients, their prognosis, and the little that there is to offer therapeutically, the factor of subjective improvement becomes important in evaluating therapy designed to treat hypertension. Ninety per cent of this group had some subjective improvement, and in 60% the improvement was considerable. However, 100% of the group had objectionable gastrointestinal symptoms; in 77% it was a major factor, and in 31% Veriloid was discontinued because of its emetic properties. The great deterrent to the use of Veriloid is the fact that the hypotensive dose and the emetic dose are almost at the same level.

If one disregards isolated improvement but considers all factors in each individual, the question arises as to whether Veriloid effected any real change in the progression of his disease. In four patients (31%) there was a marked favorable change, in two others a moderate change.

In some of the seven patients with malignant hypertension the disease was progressing at an accelerated rate prior to hospital admission and during the hospital control period. In four of these patients the progress of the disease appeared to be suspended while the patient was receiving Veriloid for periods of up to three months. It would seem that, despite the side effects of the drug, it is worthy of careful consideration as a therapeutic agent in hospitalized patients with malignant hypertension, or in nonmalignant hypertensives who have considerable hypertensive damage and severe symptoms. There appears to be no rationale for the use of Veriloid in the treatment of benign hypertensives with few symptoms and little damage.

Summary

1. Thirteen hospitalized male hypertensive patients were studied in evaluating Veriloid administered orally as a form of treatment.

2. The dosage of Veriloid employed was considerably in excess of those previously reported.

3. Seventy-seven % of the patients had significant reduction of their diastolic blood pressure, 63% had significant systolic reduction, 54% had significant reduction in both systolic and diastolic pressure, and 23% were maintained at normotensive levels.

4. The effectiveness of Veriloid appeared to be inversely proportional to the duration of hypertension.

5. Nausea and emesis were present in all of the patients, and in 77% it it was a major consideration. In 31% of the patients Veriloid was permanently discontinued because of its severe emetic effects.

6. Sixty % of the patients experienced considerable subjective improvement, and an additional 30% had some subjective improvement.

7. Veriloid administered orally appears to be useful in the treatment of hospitalized patients with malignant hypertension, or in nonmalignant hypertensives with hypertensive damage or symptoms of considerable severity. There appears to be no rationale for the use of Veriloid in the treatment of benign hypertensive patients with few symptoms and slight hypertensive damage.

ACKNOWLEDGMENT

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CASE REPORTS

NEUTROPENIA SECONDARY TO TUBERCULOUS SPLENOMEGALY: REPORT OF A CASE*

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There are few satisfactions in medicine greater than that which comes from seeing a severe neutropenia permanently reverted to normal as a result of therapy. The antibiotics have saved the lives of many of these patients during their acute infections, but the ultimate aim is to return the granulocytes to normal in number and activity. The reversible neutropenias are frequently associated with splenomegaly in which splenectomy is often curative. Such a hypersplenic mechanism, associated with a tuberculous etiology, is not common and, when present, is usually found in the disseminated or miliary form of tuberculosis. The case presented is of particular interest since the etiology of this patient's neutropenia was that of an isolated organ tuberculosis of the spleen.

Case Report

First Admission: This 58 year old white male dentist was first admitted to Hines Veterans Administration Hospital in January, 1952, because of pain in the rectal region of approximately 10 days' duration. He had had intermittent difficulty with hemorrhoids since 1943, and approximately 10 days prior to his admission had consulted his private physician because of pain in the anal area. The physician "injected something" in the area of his discomfort. The following day he noted a progression of the pain and sought hospital treatment.

In November, 1950, he had had a "bad cold" and was at bed-rest for two weeks. His maximal white blood count at that time was 6,000. In January, 1951, he was treated for pneumonia; the diagnosis was confirmed by x-ray studies. With this infection he had a white count of 5,000 with 74 per cent lymphocytes. Again in September, 1951, during a repeat episode of pneumonia, his white count varied between 3,000 and 4,000. All of these illnesses were protracted in duration, though he did have a satisfactory response after the use of antibiotics. No significant exposure to roentgen radiation in his work as a dentist could be elicited, and the only antibiotic that had been used (penicillin) was used for the aforenamed infections. He had never received chloramphenicol. A sulfa preparation was taken for the first time a few days prior to his admission in January, 1952. He denied the use of any other drugs. Difficult healing of minor abrasions and cuts received in his work as a dentist had been noted since the middle of 1950.

The physical examination revealed a moderately obese white male who appeared his stated age and was in some distress from a thrombosed external hemorrhoid. There was a diffuse erythematous induration of the right buttock adjacent to the gluteal crease radiating from a swollen, tender hemorrhoid. The spleen was pal-

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pably enlarged down to the level of the umbilicus, and the liver was palpated three to four fingerbreadths below the left costal margin in the midclavicular line.

White blood counts during this first admission varied between 1,900 and 3,900, with an average differential showing 64 per cent lymphocytes. The red blood count averaged 4,200,000, the hemoglobin, 12.5 gm. Platelet counts, urinalyses, serologic tests and x-rays of the chest were normal. X-ray studies of the abdomen revealed an enlarged liver and spleen. Bone marrow aspiration smears revealed a hyperplasia of all marrow elements.

The patient received antibiotics, and the thrombosed infected hemorrhoid was treated surgically. Recovery was uneventful, although the process was prolonged. Since the marrow was hyperplastic, it was felt that the neutropenia was due to a hypersplenic mechanism. He was advised to have a splenectomy, but the procedure was refused by the patient and he was discharged.

Second Admission: The patient was re-admitted in March, 1952, complaining of severe pain in the rectal area following bowel movements. He had continued to note poor healing of minor lacerations of his hands, and stated that his white blood count had not risen above 3,500 since discharge from the hospital. On physical examination there was no change in the size of the liver or spleen. A fissure in ano was present. White blood counts during this admission ranged between 2,200 and 4,600, and his differential count showed 48 per cent lymphocytes. X-ray of the chest again revealed no pathologic process. The fissure in ano was excised surgically and the patient was discharged from the hospital, again after refusing splenectomy.

Third Admission: He entered the hospital again in July, 1952, at which time he complained of difficulty in breathing of three days' duration, a fever of 101° F. associated with chills, a productive cough, generalized weakness and pain across the lower back. He had noted no pain on respiration. In the interval between hospitalizations there had been no improvement in his white count or in the healing of minor skin abrasions. Physical examination revealed moist crackling râles at the right base posteriorly. Findings in the abdomen were unchanged. Chest x-ray on admission revealed a pneumonitis of the right middle lobe. The white blood count at the time was 2,500, with 72 per cent lymphocytes, 26 per cent neutrophils and 2 per cent monocytes; and it remained in this range during the entire hospital stay. Liver profile studies revealed the following: van den Bergh (direct and indirect), serum albumin and globulin, alkaline phosphatase, cholesterol and cholesterol esters, and the two hour Watson test for urobilinogen were all normal. Cephalin flocculation was 4 plus in 24 and 48 hours. Thymol turbidity was 18 units initially and fell to 12 units at the time of discharge. Coombs' test was negative.

He was at first placed on penicillin therapy, and the pneumonitis slowly improved. A repeat bone marrow aspiration study revealed hypercellularity, with increased granulopoiesis with a myeloid-erythroid ratio of approximately 6:1. The patient's pneumonia cleared, both as to physical signs and on x-ray study. He again refused to consent to a needle biopsy of the liver or to a splenectomy.

The patient was then seen briefly on several follow-up examinations, at which time he continued to complain of difficulty in the healing of the small minor lacerations incurred in his work as a dentist. The white blood counts continued in the range of 2,000 and 3,000, with a predominance of lymphocytes, and the red blood count remained in the range of 4,500,000 to 5,000,000, with 13 to 15 gm. of hemoglobin and with a normal number of platelets seen in the peripheral smear. His liver and spleen size continued unchanged.

Fourth Admission: He was admitted again in January, 1953, approximately one year from the time he was first seen. At this time he complained of pyogenic lesions at the corner of his mouth which had responded only slightly to oral Aureomycin. The pyogenic dermal lesions elsewhere on the body also did not respond. A white

blood count just prior to his admission was 1,100. The physical examination revealed pyogenic lesions of the corner of the mouth and small pyodermic infections scattered about the feet and ankles. The liver was palpated three fingerbreadths below the right costal margin, with a smooth, nontender but firm edge. The spleen was palpable approximately three fingerbreadths below the left costal margin. A repeat aspiration sternal marrow study again revealed hypercellularity, with an in-

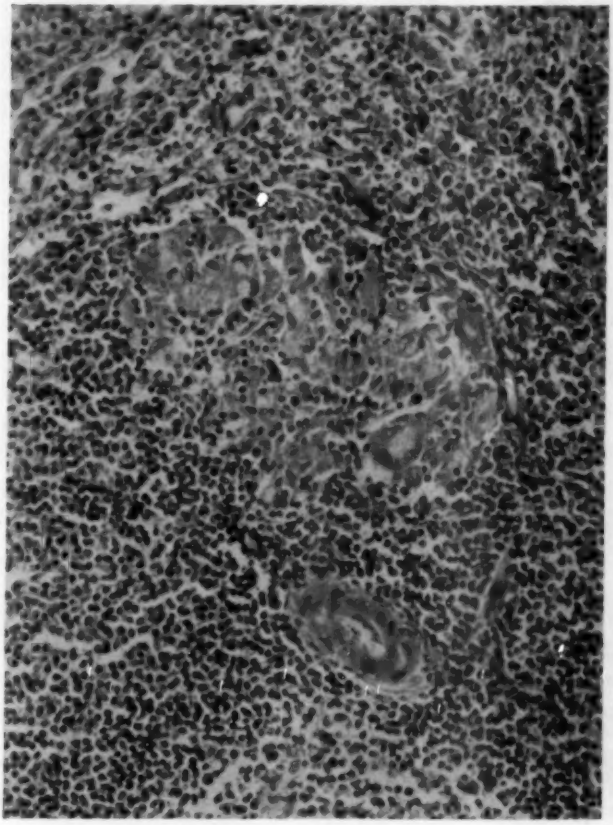

FIG. 1 *A*. Photomicrographs (see also figure 1 *B*) of the spleen showing two of the typical tubercles.

crease of the myeloid-erythroid ratio, but myelopoiesis was normal in development. There were adequate numbers of megakaryocytes forming platelets, and no cells foreign to the marrow were seen. A marked leukopenia was evident in the peripheral blood smear, with a differential count showing 74 per cent lymphocytes. Red blood count was 4,500,000. Electrocardiogram and x-ray of the chest were negative for pathology. The morning following admission a splenectomy was performed. The

white blood count the morning of surgery was 3,050, with 80 per cent lymphocytes, 19 per cent neutrophils and 1 per cent eosinophils. The red blood count was 5,250,000. Two hours after surgery the white blood count was 10,200, with 73 per cent neutrophils and 26 per cent lymphocytes. On the third postoperative day it was 13,600, and on the eighth postoperative day 17,900, with 90 per cent neutrophils, 6 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. All platelet counts

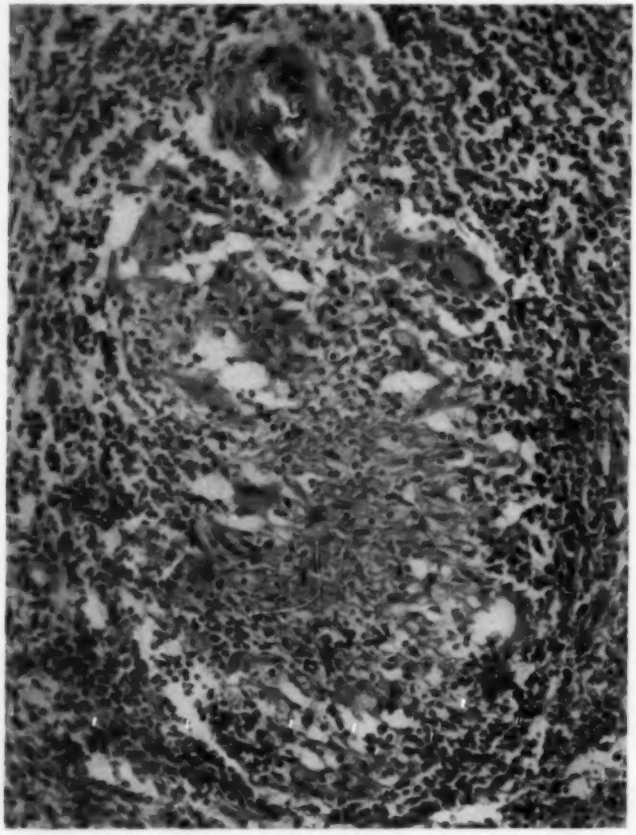

FIG. 1 *B*.

were normal. At surgery the liver was somewhat enlarged, with a finely granular surface. A wedge biopsy was obtained and on microsection revealed a well preserved architecture. There was a moderate degree of fatty vacuolation of the hepatic cells. Individual cells were well differentiated, and in the triad area there was some infiltrate with lymphocytes. The vascular channels and ducts appeared clear. Pathologic diagnosis was moderate fatty metamorphosis of the liver. The spleen measured 17 by 13 by 7 cm. and weighed approximately 1,000 gm. No accessory splenic

tissue was found. Microsection of the spleen showed the red pulp and sinusoids to be well defined. The white pulp appeared to be reduced in amount, but there were moderately enlarged germinal centers present. Several tubercles were noted composed of hypertrophied reticuloendothelial cells and a few Langhans' type giant cells (see photomicrographs). Pathologic diagnosis was tuberculosis of the spleen.

The patient's postoperative course was completely uneventful and afebrile. The skin lesions about the face cleared rapidly following the splenectomy, as did those elsewhere. The patient was discharged in good health 10 days following surgery and since has been seen frequently for follow-up examinations. His white counts have ranged between 7,000 and 11,000, and typical differential counts have been as follows: 42 per cent neutrophils, 52 per cent lymphocytes, 6 per cent eosinophils. The red count continued at 5,200,000, and platelets between 300,000 and 500,000. Sputum and gastric washing cultures for acid-fast bacilli were negative. Repeat x-ray studies of the chest have also been negative. The patient's tuberculin test was positive in strength 1 to 10,000. During the past year of his follow-up studies he has had no further symptoms of infectious lesions of the skin while continuing his occupation as a dentist. Minor abrasions and cuts now heal with normal rapidity.

Discussion

The literature [1, 3, 5, 7, 8, 10, 11] describes approximately 100 cases of tuberculous splenomegaly (that is, tuberculosis of an enlarged spleen without or with only slight tuberculosis elsewhere).[5] Winternitz [10] in 1912 studied 51 cases collected from the literature. Hematologic studies were available on 27 of these patients and revealed the presence of an anemia in 42 per cent and a leukopenia in 27 per cent during the period of observation. These findings occurred equally in both sexes and were found at all ages, but were most frequent between the ages of 20 and 40. These 51 cases of Winternitz' cannot be classed as pure tuberculous splenomegaly, for involvement in other areas was found as follows: lungs, 40 per cent (10 per cent far advanced); liver, 80 per cent; lymph nodes, 57 per cent; other organs, 66 per cent. In only one patient was tuberculosis found only in the spleen. In 1937 Engelbreth-Holm [5] reviewed an additional 28 cases and added four of his own. In two of these, tuberculous lesions were found only in the spleen, and in the others there was some involvement of the liver and nodes. His studies confirmed those of Winternitz, and he stressed the difficulty of diagnosis in the non-disseminated case prior to surgery. On gross examination, spleens in his cases did not give evidence of tuberculosis. Only on microscopic study with the demonstration of tubercles was he able to establish the diagnosis of tuberculous splenomegaly. In their case Coffee and Lipton [2] were able to make the diagnosis prior to examination of the spleen from a cervical lymph node biopsy which demonstrated tubercles. The several other reports in the literature are associated with a more diffuse tuberculous process.[4, 6, 9] The symptoms most commonly associated with tuberculous splenomegaly are intermittent fever, malaise, easy fatigability, shortness of breath, palpitation, weight loss, a dragging sensation in the left upper abdomen, and a predisposition to infection.[5] On review of the cases from which these conclusions have been drawn, it is noted that many of these symptoms have varied with the dissemination and activity of the tuberculous process. In these neutropenic patients in whom only tuberculosis of the spleen was found, often the only symptoms were those associated with the secondary infections. Such was the case in our pa-

tient—his only symptoms were those due to the local dermal or pulmonic infections.

Since preoperatively the diagnosis of tuberculous splenomegaly can rarely be made, the indications for doing a splenectomy in the hope of curing the neutropenia are those for an idiopathic hypersplenic mechanism.[3, 11] In considering such a patient for surgery the usual criteria for a good surgical risk patient (other than those findings due to the hypersplenic syndrome) should be met. In addition, there are several factors pertinent to the "splenic mechanism" that should be stressed, as they are an aid in prognosticating a good result, and great caution should be used in recommending a splenectomy if they are not present. First, the spleen should be enlarged on physical examination and, when questionable, the size should be confirmed by x-ray studies with or without the use of a barium meal. Second, the peripheral blood smear should show none of the immature cells of an acute leukemia. Third, aspiration bone marrow smears should demonstrate a full marrow with normal development of the granulocytic and erythrocytic elements, and megakaryocytes should be present in adequate numbers showing evidence of platelet formation. In the absence of these criteria, especially a full marrow, the results from splenectomy are often disappointing.[3, 11]

As in other reports,[5, 10] the spleen in this case was also grossly normal, and only on histologic study were tubercles found. No gross tuberculous lesions were noted in the liver at the time of surgery, and a wedge biopsy failed to reveal tubercles on multiple sections. Tuberculous nodes were not found in the abdomen. Immediately following splenectomy there was a disappearance of the neutropenia that the patient had had, unassociated with depression of other blood elements, for several years. Since the return of the granulocytes to normal levels, he has remained free of the many infections which before were so frequent and persistent. Though during the 14 months' follow-up period to date there has been no clinical or laboratory evidence of a tuberculous process elsewhere, it seems reasonable to assume that the splenic tubercles were probably seeded from a small pulmonary focus now inactive or healed.

Summary

A case of neutropenia associated with splenomegaly has been presented. Splenectomy was performed and the patient had a rapid and definite response, with elevation of the total white count and increase in the number of circulating neutrophils. Microscopic sections revealed tuberculosis of the spleen and fatty metamorphosis of the liver. No other clinical or laboratory evidence of tuberculosis has been found.

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INFECTIOUS MONONUCLEOSIS ENCEPHALITIS: CASE REPORT *

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INTRODUCTION

ALTHOUGH infectious mononucleosis is a fairly common disease, central nervous system involvement occurs in only 0.7 to 1.0% of cases.[1, 2] Encephalitis as a complication has been reported to date in only 15 cases.[3] Since the neurologic features may be so outstanding on occasion, the primary disease process may remain obscure for some time. It is the purpose of this communication to report another case of infectious mononucleosis encephalitis ushered in by psychotic manifestations.

CASE REPORT

This was the first Queens General Hospital admission of a 22 year old white female airline stewardess, who entered the hospital on January 11, 1954, in a disoriented and confused state. The patient was unable to give a history, and the pertinent information was obtained from the patient's roommate.

Present Illness: On January 3 the patient developed tender, swollen glands in her neck bilaterally. The lymphadenopathy did not subside and, while the patient did not feel well, she did not feel ill enough to stop flying between New York and Chicago. She had never been outside of the United States. On January 7 she returned to New York. On the afternoon of January 9 the roommate noted that the patient appeared confused and lethargic, and incapable of arriving at a decision as to whether she should fly that evening. The roommate advised against flying and managed to get the patient to eat a light supper and go to bed.

The following day the patient was noted to be even more lethargic and occasionally irrational. It also became apparent that she experienced considerable instability when she tried to walk. She began to vomit, and her temperature was 102.5° F. (oral). When seen by a physician she was completely unresponsive and uncoöperative; psychiatric consultation was advised.

That evening the temperature rose to 103° F. (oral), and vomiting became more frequent. Another physician was called, a diagnosis of "strep throat" was made, and an injection of penicillin was given. The temperature ranged between 101.5° and

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From the Department of Internal Medicine, Queens Hospital Center, Queens General Hospital, Jamaica, N. Y.

TABLE 1
Heterophil Agglutination Titers

Non-absorbed		Absorbed			
Date	Titer	Date	Non-absorbed	Absorbed Guinea Pig Kidney	Absorbed Beef RBC
Jan. 11	1:1224	Jan. 13	1:3584	1:1792	1:0
Jan. 26	1:1024	Jan. 25	1:1792	1: 896	1:0
Feb. 15	1: 64				

102.5° F. (oral) during the early morning hours of January 11. Mental confusion increased, and at times the patient lapsed into coma. Hospitalization was advised, and the patient was admitted to Queens General Hospital.

Past History: The past history and system review were noncontributory. The patient had received no injections or inoculations during the previous year, and aside from the present illness had been perfectly well.

Physical Examination: Temperature, 101.8° F. (rectal); pulse, 100; respirations, 20 per minute; blood pressure, 112/85 mm. of Hg. The patient was a young, well

TABLE 2
Liver Function Studies

Date	Ceph. Floc.	Thymol Turbid.	Alk. Phos. K.A.U.	Total Bilirubin	A/G	Chol. Esters	BUN
Jan. 13	4+	10.8	3.0	0.3	4.1/2.9	—	5
Jan. 15	—	—	—	0.5	—	97/64	—
Jan. 18	4+	11.6	6.0	0.2	3.5/2.0	—	—
Jan. 25	4+	16.5	7.5	0.4	4.5/1.6	192/140	5
Feb. 15	Neg.	6.6	1.2	—	—	—	—

developed, well nourished white female who was acutely ill, confused, disoriented and irrational, and was babbling constantly and incoherently. The head, ears and nose were normal. The pupils were equal and responded to light. The fundi were normal. The patient refused to open her mouth. Bilateral small cervical nodes about 2 to 3 mm. in diameter were present. No axillary, inguinal or epitrochlear nodes could be palpated. The heart and lungs were normal. The liver, spleen and other abdominal organs could not be palpated. The neurologic examination revealed the cranial nerves to be intact. Deep tendon reflexes were hypoactive but equal. There was no detectable muscle weakness in the extremities. The neck was not stiff;

TABLE 3
Spinal Fluid

Date	Pressure Mm. H_2O	No. Cells Type	Prot. Mg. %	Sugar Mg. %	Cl. mEq./L.	Coll. Gold.	Cult.	Hetero-phil	Wass.
Jan. 11	180	55 polys	272	10	147	flat	ster.	1:8	Neg.
Jan. 13	200	46 lymphs	132	78	119	flat	ster.	—	Neg.
Jan. 18	180	12 lymphs	94	—	122	flat	ster.	—	Neg.
Jan. 25	90	6 lymphs	81	42	128	flat	ster.	4+*	Neg.

* Spinal fluid heterophil according to the method of Silberstein, Bernstein and Stern.[11]

TABLE 4
Viral and Bacterial Studies

Viral Studies: Antigen	Control Date Jan. 12	Test Date Jan. 21
Lymphocytic choriomeningitis	Negative 1:4 Dil.	Negative 1:4 Dil.
Eastern equine encephalitis	Negative 1:4 Dil.	Negative 1:4 Dil.
Western equine encephalitis	Negative 1:4 Dil.	Negative 1:4 Dil.
St. Louis encephalitis	Negative 1:4 Dil.	Negative 1:4 Dil.
Japanese B encephalitis	Negative 1:4 Dil.	Negative 1:4 Dil.
Mumps	Positive 1:8 Dil.	Positive 1:8 Dil.

Serum or Weil's reaction: *Lept. icterohaemorrhagiae, Lept. canicola, Lept. pomona* negative on January 12 and January 21.
Numerous blood and urine cultures sterile.
Mantoux, negative up to 1:1000.

Kernig's and Babinski's signs were not present. The mental status was as mentioned above.

Laboratory: Urinalysis revealed a trace of acetone but was otherwise negative. Hemoglobin, 12 gm., white blood count, 11,800, with 71% polymorphonuclear cells, 21% lymphocytes and 8% monocytes. No atypical cells were observed. A spinal tap revealed clear fluid with an initial pressure of 190 mm. water, and a cell count of 50 polymorphonuclear cells per cubic millimeter. Spinal fluid protein was 272 mg. %; chlorides, 147 mEq./L., and sugar, 80 mg. %. Gram stain revealed no bacteria. Roentgen studies of the chest, skull and mastoids were negative. A scout film of the abdomen demonstrated no enlarged liver or spleen.

Blood and urine cultures, control viral studies, liver chemistries and heterophil agglutination specimens were obtained, and a first strength Mantoux was done. In view of the possibility that an early meningitis had been masked by the previous penicillin, the patient was started on aqueous penicillin, 3,000,000 units every two hours, and sulfadiazine, 1.0 gm. every four hours.

Course: During the next 24 hours the patient's level of unconsciousness became deeper, progressing to complete coma, with Cheyne-Stokes respiration and urinary retention. Because of the patient's moribund condition and the obscurity of the etiology, Terramycin, streptomycin, and Isonicotinic acid hydrazide were started. The Cheyne-Stokes respiration was well controlled with aminophylline suppositories.

On the third hospital day a repeat spinal tap revealed clear fluid under normal pressure, with a cell count of 46 lymphocytes per cubic millimeter. The protein was 132 mg. %; chlorides, 79 mEq./L., and sugar, 78 mg. %. The heterophil agglutination titer returned and was 1:1224. A second blood count disclosed a hemoglobin of 11.3 gm. and a white blood count of 13,300 cells per cubic millimeter, with 48% polymorphonuclear cells, 9% normal lymphocytes, 21% abnormal lymphocytes (Türk's

TABLE 5
Peripheral Blood

Date	Hb.	WBC	Polys	Normal Lymphs	Türk's Cells	I.M. Cells	Monos.	Eos.
Jan. 11	12.0	11,800	71	21	0	0	8	0
Jan. 13	11.3	13,300	48	9	21	22	0	0
Jan. 15	11.0	10,200	59	11	22	8	0	0
Jan. 19	10.5	6,300	44	17	23	12	0	0
Feb. 15	13.1	8,800	69	24	0	0	5	2

cells), and 22% infectious mononucleosis cells. The first blood smear was reviewed and it was concluded that a diagnosis of infectious mononucleosis could not have been made from it. Repeat heterophils were drawn for absorption studies, and these results are tabulated in table 1. All antibiotics were discontinued except Terramycin, which was continued because of an indwelling catheter.

Improvement began on the fourth hospital day and the patient took several glasses of fluid by mouth. Although she spoke occasionally, she was aphasic and still refused to allow visualization of her throat.

The next day her deep tendon reflexes returned to normal and she spoke on occasion at great length, but her behavior was quite childish. She allowed her throat to be examined, and it was found to be normal. The indwelling catheter was removed but had to be replaced because of persisting retention. Aminophylline suppositories were still found to be necessary to control the respiration.

The following day the patient's improvement was truly dramatic, with complete clearing mentally. She requested and took fluids without difficulty. The catheter was removed; aminophylline and Terramycin were no longer required. Visual fields were normal. An electroencephalogram showed diffuse 4 to 6 second activity, with bursts of 3 per second activity of high amplitude. The record was symmetric, with no evidence of focalization. It was consistent with markedly diffuse pathology, as seen in infectious or toxic states. At this time results of chemical liver function

TABLE 6

Electrolyte and Minor Serologic Studies

Serum sodium, potassium, chloride and carbon dioxide all within normal limits.
Wassermann tests on January 11, January 18 and February 15, negative.
Coombs' test, negative. Antibodies on serum: cold (5°C.), positive; warm (37°C.), negative.
Cold agglutinins of January 14 and January 21, both 1:20.

tests returned and were abnormal. They are summarized in table 2. Repeated electrocardiograms failed to show any abnormality.

The rectal temperature during the course of the illness ranged between 100° and 102° F. On January 16 it began to fall by lysis, and on January 18 returned to normal. On January 27, after 17 hospital days, the patient was discharged. Follow-up laboratory data are listed in the tables under the date February 15, 1954. The patient is completely well, and returned to full duty in March, 1954.

DISCUSSION

The clinical picture of infectious mononucleosis without nervous system involvement may mimic many other diseases.[4] This also holds true for infectious mononucleosis when the nervous system is involved and, indeed, it must be considered whenever the diagnosis of aseptic meningitis is entertained.[5]

In addition to the triad of clinical, hematologic, and serologic criteria for the diagnosis of infectious mononucleosis, a fourth criterion must be added, namely, evidence of liver dysfunction.[2]

The clinical and hematologic aspects of the disease have been well described.[6, 7]

The sheep cell agglutination test is of great diagnostic importance and, if serum sickness can be ruled out, a titer of 1:1792 may be accepted as diagnostic for infectious mononucleosis, even in the absence of absorption studies.[3] With

titers below this, absorption studies are necessary in order that the titer be significant. Although four cases have been reported of high titers (above 1 : 1280) in diseases other than infectious mononucleosis, there is some question as to whether infectious mononucleosis was not really present as well, and the reports are not at all conclusive.[8, 9, 10]

The spinal fluid Wassermann is negative, but occasionally there is an abnormal colloidal gold curve. The spinal fluid heterophil agglutination in this case was negative when done in the usual manner. This agrees with the findings of Bernstein and Wolff.[1] However, Silberstein, Bernstein and Stern [11] have demonstrated heterophil antibodies in cerebrospinal fluid in six patients with infectious mononucleosis when done by their modification of the heterophil agglutination test. With their method, the cerebrospinal fluid was positive for infectious mononucleosis in this patient. Aside from the serologic aspects of the spinal fluid, there is usually a pleocytosis and/or an increase in protein. The cells are usually increased to only a moderate degree and are mainly lymphocytes, none of which to our knowledge has ever resembled the abnormal forms found in the peripheral blood. It is noteworthy that in this case the initial spinal fluid revealed all polymorphonuclear cells, while the protein was elevated, and chloride and sugar levels were within normal limits. However, subsequent spinal taps revealed lymphocytes.

The fact that the blood Wassermann test often shows a false-positive in this disease is well known.[4]

The fourth criterion for the diagnosis of infectious mononucleosis is deranged liver function tests. In studies by Gall [12] in 1947 and Evans [13] in 1948, abnormality of the alkaline phosphatase, cephalin flocculation and thymol turbidity tests have been described. In a review of the literature up to 1953 [2] it was found that abnormal liver function tests were present in 40 to 100% of cases. In the case herein presented the thymol turbidity and cephalin flocculation tests were deranged, while the alkaline phosphatase remained within normal limits.

It is interesting to note that, aside from the initial physical symptoms in this case, the illness manifested itself by signs of a psychosis. This manifestation of the disease is quite rare but has been reported.[5, 14] Involvement of Broca's speech area has been described,[15] and we believe this area was involved in this patient, as manifested by aphasia. Unfortunately, the patient in this case report was too ill to have an early electroencephalogram done. However, the electroencephalogram done on the fourteenth day of the illness was abnormal.

Respiratory distress became apparent in this patient soon after admission, and Cheyne-Stokes respiration lasted throughout the first few days of illness. In the cases of infectious mononucleosis encephalitis that have died, respiratory arrest seems to have been the main cause.[2]

Summary

A case of infectious mononucleosis encephalitis is reported that meets the four criteria necessary for such a diagnosis. Serologic tests, spinal fluid and liver function tests are discussed briefly, as is the unusual way in which this patient presented herself to the hospital. Tables summarizing the laboratory data are included.

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EXTENSIVE FIBROPLASTIC PERITONITIS SECONDARY TO PROTRACTED ACUTE PANCREATITIS*

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THE clinical and pathologic picture presented by acute hemorrhagic pancreatitis may be extremely variable. Frequently listed among the protean manifestations of the disease are paralytic ileus, shock, hypocalcemia (occasionally to the point of tetany), hemorrhagic ascites, and abdominal masses (pseudocysts or abscesses). Reported more rarely are severe diabetes mellitus early in an attack,[1] hyperlipemia,[2] pleural effusion,[2] hemothorax,[3] massive hemorrhage into

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peripancreatic tissue or in remote areas of the body with melena, hematemesis, hematuria, or even mediastinal or subcutaneous bleeding,[2] retroperitoneal dissection into the pelvis,[4] acute colonic obstruction,[5] mechanical small-bowel obstruction due to fibrous bands,[2] and perforation of the right colon.[2] Cursory examination of the medical literature reveals only occasional brief references to localized chemical peritonitis following acute pancreatitis. A single case report was discovered of a patient with acute pancreatitis dying of massive intra-abdominal hemorrhage in whom was noted incidentally at autopsy a "plastic peritonitis involving particularly the small intestine." [1] This rarely reported complication has been noted also by Gambill, Baggenstoss et al. in a patient dying after 17 days of acute hemorrhagic pancreatitis, in whom 3,000 c.c. of ascitic fluid accumulation were found, with intestinal coils matted together by fibrinous adhesions.[6] It would seem of interest, therefore, to present a recent case of acute pancreatitis with a protracted, complicated course and a fatal termination in large part brought about by the sequela of extensive fibroplastic peritonitis, with constriction of the entire intestinal canal. This case is further noteworthy because of the unusually prolonged elevation of serum amylase, the considerable accumulation of sanguineous ascitic fluid, and the transient but dramatic clinical improvement following intravenous infusion of human albumin.

Case Report

A 34 year old white married draftsman was admitted on July 2, 1953, because of epigastric pain of five months' duration. He had been a heavy alcoholic for 12 years, with poor nutritional intake for two years. During the preceding year palmar erythema, spider angiomata and decreasing libido had been noted. Five months prior to admission he began to have frequent "indigestion," characterized by vague epigastric pain and eructations, usually in the early evening. During the last two weeks this pain had become continuous, and he began to vomit bile-stained material every other day, which on several occasions contained one-half cupful of "dark blood." About six weeks before admission swelling of the ankles occurred; this disappeared on a low-salt diet. One week before entry the abdomen became distended. For four days he had loose stools, without melena. He had lost 20 pounds in the six months prior to admission, but had continued to work. There had been no jaundice, change in color of urine or stool, fever or chills.

Physical Examination: Temperature, 99° F.; pulse, 110; respirations, 22; blood pressure, 108/86 mm. Hg; weight, 132 pounds. The patient was a well developed, thin, tremulous white male, appearing chronically ill, not icteric. Marked palmar erythema and spider angiomata were noted. Heart and lungs were normal. There was moderate abdominal distention, with prominent venous pattern, fluid wave and shifting dullness. Peristalsis was slightly hypoactive. No abdominal organs or masses were felt. The testicles were bilaterally atrophic. Feces were brown and guaiac-negative. There was no peripheral edema.

Laboratory Data: Urinalyses were normal. Serology was negative. White count, with normal differential, was 13,300 on admission, and thereafter ranged between 7,000 and 16,500. Hematocrit was 42 per cent on admission, falling to 32 per cent on the twelfth day and thereafter stabilizing between 34 per cent and 38 per cent. Nonprotein nitrogen was 36 mg. per cent; serum bilirubin concentration, 0.8 mg. per cent; cephalin flocculation, 0 to 3 plus (48 hours); thymol turbidity, 1.3 units; prothrombin time, 40 to 100 per cent; alkaline phosphatase, 4 to 9 units; Bromsulphalein retention, 10.4 per cent; amylase, initially 297 units (modified Somogyi method—normal, 50 to 150 units), and remaining generally elevated through-

out (figure 1). Total serum protein was 4.8 gm. per cent, with albumin 1.3 gm. per cent initially; albumin, 2.1 gm. per cent after infusion of 100 gm. of human albumin; total protein, 6.1 gm. per cent (albumin, 2.6 gm. per cent) on eighty-second day. Na^+ was 126 mEq./L. and Cl^- was 86 mEq./L. initially, both falling lower and remaining low (except for transient rises after hypertonic saline infusions); CO_2, 23.2 to 18.7 mEq./L.; K^+, 4.0 to 6.3 mEq./L.; and Ca^{++}, 9.0 mg. per cent. *Sputum cultures:* normal flora; negative for tubercle bacilli. *Ascitic fluid examinations* (× 5) revealed specific gravity of 1.004 to 1.007; total protein, 2.2 to 3.1 mg. per cent; red cell count, 200,000 to 400/mm.^{3}; white cell count, 700 to 200/mm.^{3} (61 per cent polymorphonuclears initially; 27 to 30 per cent polymorphonuclears thereafter); fluid amylase, 412 to 463 units; cell block, negative (× 3); routine cultures (× 5) showed no growth; cultures and guinea pig inoculation for tubercle bacilli were negative (× 3). *Electrocardiogram* (sixty-second day) suggested hypokalemia. *X-rays:* Chest films: On admission, normal; fifth day, slight blunting of right costophrenic angle; nineteenth day, moderate amount of fluid at right base; thirty-third day, diminution in right basal fluid; throughout hospitalization, left lung

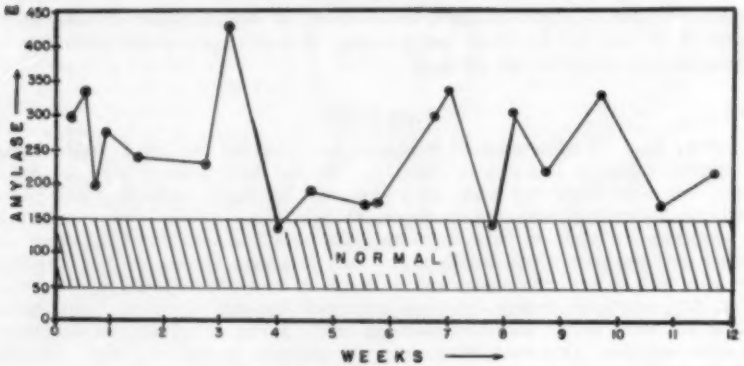

FIG. 1. Serum amylase levels.

field clear. Gastrointestinal series on admission: negative, except for small hiatus hernia. Abdominal films: third day, small-bowel dilatation with barium in small-bowel loops; fifth day, fluid levels seen in dilated loops of small bowel; thirteenth day, ascitic fluid accumulation.

Hospital Course: On a milk diet, gelusil and belladonna the patient was moderately comfortable and afebrile for two days but then began to complain increasingly of severe epigastric pain, to vomit bile-stained material, and to run a fever to 101° (rectal). Vomiting on the fourth day became profuse and foul, epigastric pain was more severe, and the abdomen was distended, diffusely tender and tympanitic, with marked hypoperistalsis. With his abdominal film indicating small-bowel ileus and amylase suggesting pancreatitis, the patient was treated with constant gastrointestinal suction by Miller-Abbott tube, nothing by mouth, and intravenous fluids. Atropine, 0.6 mg. subcutaneously every six hours, and intramuscular vitamins, as well as penicillin and streptomycin, were started. With this program, pain became less, vomiting subsided, and bowel sounds slowly improved; the small bowel by x-ray was seen to empty of barium. On the fifth day, left anterior chest pain of pleuritic nature occurred, with a loud pleural friction rub transiently heard (24 hours). By the sixth

day the patient was more comfortable and afebrile; on the seventh day, intubation and suction were discontinued and on the eleventh day he was started cautiously on oral feedings. During the first 10 days, abdominal fluid increased and edema of legs and genitalia appeared, with a 23 pound weight gain. Hypertonic saline given twice during this period neither corrected persistent hyponatremia nor effected diuresis. Paracenteses were at first small and only for diagnostic purposes, until a third tap performed on the eleventh day yielded 8 L. of reddish brown sanguineous fluid. From the third to the ninth week the patient ran an irregular course, characterized by episodes of severe epigastric pain requiring Demerol analgesia, abdominal tenderness and distention, vomiting, low-grade fever, and intermittent need for parenteral nutrition and hydration. During the fifth week following repeat paracentesis, 100 gm. of salt-free albumin were given intravenously. At that point transient loss of edema occurred, as well as definite clinical improvement, with oral nourishment once again taken moderately well, and with diminution in pain allowing temporary abandonment of Demerol analgesia. In the sixth week, when peripheral edema was minimal, the patient had a second brief episode of pleuritic pain, with loud pleural friction rub over the left anterior chest, with chest film negative and with the patient remaining afebrile. During the last six weeks, although afebrile, the patient had severe epigastric pain requiring continuous analgesia. Left splanchnic nerve block brought no relief. By the ninth week, edema and ascites had again increased; the patient appeared more ill and emaciated. Oral intake was discontinued and parenteral hydration was resumed; further infusions of plasma and attempts to adjust electrolytes were found ineffective. Vomiting of small amounts continued. He became increasingly lethargic and emaciated, and died quietly on the eighty-sixth hospital day.

Autopsy Report: Gross Findings: Examination of the *body* revealed a greatly emaciated white male with pitting edema of the left leg and right ankle. Examination of the *peritoneal cavity* after opening the tensely distended abdomen showed 7,100 c.c. of dark green-yellow fluid. The peritoneal wall was yellow-pink to gray, and showed marked venous distention. The most striking finding was the marked reduction in volume of the entire bowel, collapsed, compressed, and matted together against the posterior wall under fibrous adhesions such that the abdominal cavity appeared quite empty, the bowel occupying perhaps one fourth or less of its volume. The pelvis contained no bowel except for the thin narrowed rectum and sigmoid clinging to the left wall. Inspection of the *pleural* cavities showed no fluid or adhesions on the right, but on the left there were 175 c.c. of dark red viscid fluid mixed with a large amount of mucopurulent yellow-green material. The *lungs* were of interest because of the finding in the left lower lobe posterolaterally of a large hemorrhagic infarct, dark red, 6.5 by 10.0 cm., in the center of which was an abscess 1.2 by 0.4 cm. containing viscid yellow-green fluid, with a firm pyogenic lining membrane. *Heart and great vessels* were normal except for an organized thrombus adherent to the intima of the inferior vena cava for a distance of 2.6 cm. above the bifurcation, continuing for 3.2 cm. into the right and left common iliac veins and almost occluding their lumina. The *spleen* weighed 100 gm. and had a corrugated gray-blue capsule. The *pancreas,* reduced to one third its normal size, weighed 35 gm. and was firm in consistency, its surface mottled with light gray patches, with severe distortion of the lobular architecture (cut surface), and with the ducts almost completely filled with inspissated soft gray material. The *esophagus* was free of varices. The entire small and large *bowel* was severely knotted and compressed by fibrous tissue, as described above; bowel mucosa appeared grossly normal. The *liver* weighed 1,050 gm. Its entire anterior aspect was covered with a thick, 1 mm. layer of yellow fibrous tissue with a rough uneven surface. The vascular structures of the porta hepatis were encased in a sheath of fibrous tissue. The capsule was corrugated and finely nodular. The liver was firm, its cut surface red-brown, with the lobular

structure intact in most areas. Thin yellow-white bands of fibrous tissue ran through the lobules. The *gall-bladder,* small and contracted and filled with golden viscid fluid, was free of stones and had patent bile ducts. The *testes* were atrophic. The *kidneys, brain, thyroid,* and the remainder of the gross examination were negative.

Microscopic Findings: Lungs: Sections of the left lower lobe infarction, with an abscess which had broken through the pleura in two places, showed interstitial fibrosis with a layer of old fibrin on the pleura, suggestive of advanced organization. Elastic tissue stains confirmed the impression that the infarct was about two months old. *Veins:* Sections through the lower vena cava and the iliac veins suggested old thrombosis of the left common iliac vein with some recanalization, and recent thrombosis of the right common iliac vein and the lower vena cava. *Spleen:* A thick layer

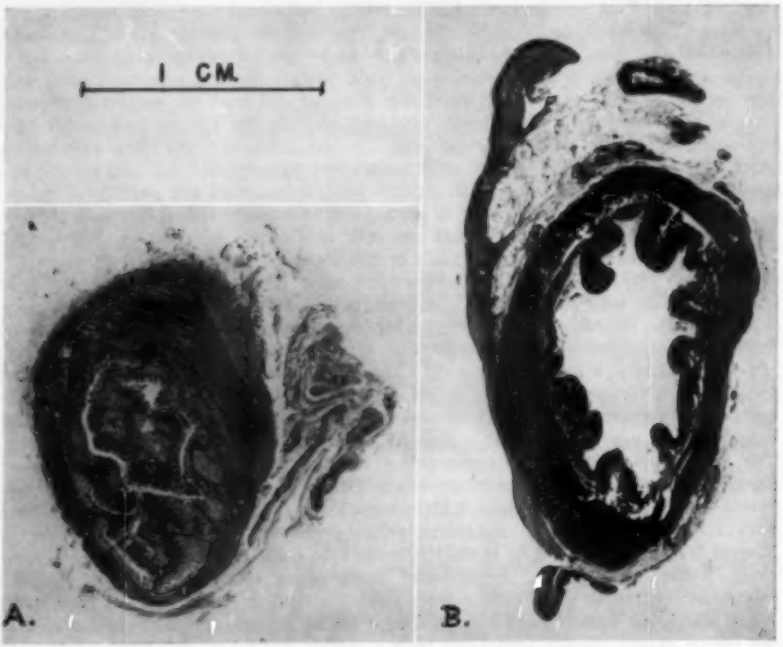

FIG. 2. Complete cross-sectional views of constricted bowel. (A) Jejunum. (B) Colon. (Magnification approximately fourfold. Note scale above.)

of old fibrous tissue was seen over the peritoneal surface, with the underlying capsule slightly wavy. *Pancreas:* The larger ducts were dilated (2 by 5 mm.), and loosely filled with deeply eosinophilic masses of inspissated secretion, without lamination or calcification. Many interstitial pseudocysts (up to 8 by 2 mm.) were noted, with wide bands of scar tissue throughout. Hematoidin was present in fibrous tissue adjoining the cysts. Acinar tissue was more than half preserved, but the individual acini were small and some of the lobules were completely replaced by fibrous or fat tissue. Minute foci of fat necrosis were observable. No evidence of cancer was found in sections of pancreas or adjacent lymph nodes. *Esophagus:* Multiple small, pitlike ulcerations of the mucosa were seen, with infiltration by polymorphonuclears and fibrin. *Stomach:* In sections of the pyloric antrum fibrous serosal thickening

was noted, as well as a zone of edema in attached fat tissue, diffusely infiltrated with polymorphonuclears and macrophages. The serosal fibrous tissue contained a lenticular focus of eosinophilic material, plus red blood cells and a few polymorphonuclear cells, with traces of hemosiderin. A *jejunal* cross-section, 11 by 6 mm.

FIG. 3. Section through thickened serosa of colon showing laminated fibrosis (H&E × 65).

in complete size, showed lumen largely filled by crowded mucosal folds, with serosa greatly thickened by fibrous tissue rich in capillaries but devoid of leukocytic infiltration (figure 2 A). A complete cross-section of *large intestine* measured 10 by 16 mm., not including a serosa thickened by dense fibrous tissue 1 mm. thick, containing a few macrophages and lymphocytes (figures 2 B and 3). The fibrous tissue was laminated parallel with the serosal surface, with narrow masses of old, dense, deeply eosinophilic fibrin between some of the laminae. The *appendix* was covered by a dense layer of fibrous tissue with traces of hemosiderin. *Liver:* Old fibrous layer on the surface was again noted. There was uniform slight increase in periportal fibrous tissue, with no alteration of the hepatic architecture. The liver cells generally appeared somewhat small and atrophic. *Testes:* Marked reduction in spermatogenesis was seen. *Gall-bladder, adrenals, kidneys* and *brain* were normal on microscopic examination.

Pathologic Diagnoses: General: Marked emaciation. Edema of ankles and left leg. Ascites. Chronic fibrous peritonitis, nonspecific, with compression of small intestine, spleen and other viscera. *Cardiovascular:* Old thrombosis and recanalization of left iliac vein. Recent thrombosis of right iliac vein and lower inferior vena cava. *Respiratory:* Purulent tracheobronchitis and bronchopneumonia. Pulmonary infarct, left lower lobe, with central abscess rupturing into pleural cavity. Sanguineous empyema, left, and organizing fibrinous pleuritis. Fibrous pleuritis, right. *Gastrointestinal:* Acute esophagitis. Subacute phlegmonous perigastritis and antral gastritis, ? secondary to pancreatitis. Chronic pancreatitis, with pseudocysts, secondary to duct obstruction. Laennec's cirrhosis, slight. *Genitourinary:* Atrophy of testes, early, with aspermatogenesis.

Discussion

Upon admission, this tremulous, malnourished alcoholic with a two-week history of continuous epigastric pain, vomiting and slight hematemesis was thought to have decompensated hepatic cirrhosis, with ascites and edema. Bleeding from ulcer, gastritis or even esophageal varices was feared. Negative gastrointestinal series, normal liver function tests, developing paralytic ileus, bloody ascitic fluid and elevation of amylase in serum and abdominal fluid changed the primary diagnostic impression to acute hemorrhagic pancreatitis, and the therapeutic approach was correspondingly altered. As the prolonged course continued downhill, with further emaciation and unremitting epigastric pain, the diagnosis of carcinoma of body or tail of the pancreas was seriously entertained by many observers. However, when death occurred at 12 weeks, autopsy revealed pancreatitis of some duration, extensive fibrous peritonitis, minimal hepatic cirrhosis, old left pulmonary infarct, and old left iliac vein thrombosis.

In most cases of acute pancreatitis, serum levels of amylase return to normal within 24 to 72 hours.[7, 8] Sustained high levels are associated with continuation, extension or progression of the acute process,[7] and return to normal may be delayed by such complicating activity for days or weeks.[9] Elevation of serum amylase for longer than five days was seen in five of 86 cases of acute hemorrhagic pancreatitis studied by Olander et al.,[10] the most prolonged duration of elevation being 46 days. In our case, significant elevation of serum amylase continued for 82 days (figure 1), with peritoneal fluid amylase measured on three occasions (through the sixty-eighth day) and found always to be 35 per cent to 50 per cent higher than that of the serum. Persistence of high amylase values in addition to continued severe epigastric pain suggested continuation of the obstruc-

tive and inflammatory process in the pancreas, and might have predicted the degree of pathologic involvement of that organ, since glands having only moderate necrosis and hemorrhage are generally the ones able to maintain enzyme formation, thus sustaining amylase levels until death.[9] The possible slight contribution of the employment of Demerol[11] in this case, or of the secondary fibrous peritonitis itself,[12] in augmenting the serum amylase level, must be considered.

The mechanism of considerable ascites formation in this case is worthy of speculation. Ascites is not an uncommon complication of severe acute pancreatitis,[6] probably dependent upon the intensity or extensiveness of the peritoneal inflammatory process, with consequent exudation and often hemorrhage. Usually peritoneal fluid accumulation amounts to from a few hundred to less than 2,500 c.c. of red-brown fluid. In our case the marked and rapidly recurrent ascites was probably in large part secondary to the severe hypoalbuminemia, with right pleural effusion and peripheral subcutaneous edema other manifestations of this condition. Prolonged malnutrition to the point of virtual starvation in this chronic alcoholic was an important factor leading to protein depletion; continued starvation aggravated by his pancreatitis, loss of protein into the peritoneal cavity by exudation and transudation, and protein removal by abdominal paracentesis were other factors. An additional etiology for the marked ascites here might be seen in Karsner's statement that chronic peritonitis in itself may produce ascites by damming lymphatic outflow.[13] Other possible causes for ascites were not found. No significant hepatic cirrhosis could be demonstrated to contribute to the protein deficiency, or to produce portal hypertension; kidney function and morphology appeared intact; infection or peritoneal implants of tumor were not present; and extrahepatic portal vein obstruction was not evident at autopsy.

The left pleuritic chest pain, with audible pleural friction rub present on the fifth hospital day, was thought to represent inflammation of the diaphragmatic and basal parietal pleura resulting from chemical irritation by pancreatic enzymes conveyed via transdiaphragmatic lymphatics, as has been reported.[2, 6] Pleuritic pain and loud friction rub in the same area were transiently noted again several weeks later, seven weeks prior to death. The small organized pulmonary infarct found at necropsy, however, was probably the basis for at least this second bout of pleuritic chest pain.

The most striking feature of our case was the extensive fibroplastic peritonitis that had caused marked compression of the entire intestinal canal as well as of all abdominal viscera, with the matted, knotted small bowel covered with a thick gray veil of fibrous tissue, leaving the peritoneal cavity largely empty. Descriptions of such an extensive, advanced process resulting from chemical inflammation and exudation in acute pancreatitis have not been found in the medical literature. Low-grade infection as a cause has been ruled out by repeatedly negative cultures and acid-fast studies, as well as by microscopic sections. Not only may this extensive reaction have contributed to the ascites accumulation,[13] and even perhaps in some degree to the persistent amylase elevation,[12] but it also without doubt played some part in the unrelenting abdominal pain not relieved by left splanchnic nerve block, as well as a major role in the vomiting, poor oral intake, reduced intestinal absorption, and thus the continued starvation and ultimate death of the patient. Figure 2A demonstrates well the intestinal compression and marked luminal narrowing by the thick, organized exudate.

The best period of symptomatic improvement, with transient diuresis, lessening of edema, subsidence of pain, brief resumption of oral intake without vomiting, and short-lived dip in amylase level followed the intravenous infusion of 100 gm. of salt-free albumin early in the fifth week. This therapy was attempted because of the marked hypoalbuminemia, which was thereby partially corrected. In retrospect, other good indications for albumin therapy may have existed. It has been recently reported that severe malnutrition and protein deficiency may play a primary role in the production of acute pancreatitis,[11, 14] and hence that protein replacement may be a specific therapeutic weapon. Furthermore, on the basis of both animal experimentation and 11 consecutively treated human cases of acute pancreatitis, Kenwell and Wells report "impressive clinical evidence of improvement" and markedly reduced mortality with treatment featuring infusions of salt-free albumin.[15] The rationale here is based on Landsteiner's discovery in 1900 of an antitryptic factor in serum albumin; it is hoped that albumin may be an effective inhibitor of the spontaneous activation of trypsinogen to trypsin in living tissue.

Although not used in this case, cortisone might have been of some value in therapy. Stephenson has enthusiastically reported its use in a case of acute pancreatitis who, on admission, was in shock, febrile and moribund, and yet who dramatically recovered.[16] Conceivably the exudative changes and later constricting fibrous reaction might have been less intense if our patient had received this drug.

The old and organized thrombus of the left iliac vein and more recent thrombosis of the lower inferior vena cava are thought related simply to circulatory stasis in a cachectic, bed-ridden patient with marked ascites, and probably not to have significance from the point of view of pancreatic inflammatory disease.

Summary

A case has been presented of protracted acute hemorrhagic pancreatitis in a young malnourished alcoholic in whom, at autopsy, after three months of this illness, an extensive fibroplastic peritonitis compressing the entire intestinal canal was found. Other noteworthy features included elevation of serum amylase for 12 weeks, and the considerable accumulation of sanguineous ascites. These findings and certain therapeutic considerations are discussed.

Acknowledgment

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*LEPTOSPIRA GRIPPOTYPHOSA**

By EDWIN E. GOLDBERG, M.D., HAROLD B. SHRIFTER, M.D., and MURRAY FRANKLIN, M.D., F.A.C.P., *Chicago, Illinois*

LEPTOSPIRAL diseases have been for many years considered uncommon in the United States and have therefore not received their due attention in medical colleges or in clinical medicine. However, an increasing awareness of the importance of leptospirosis in human and animal disease is attested to by the numerous reports on this subject appearing in the literature in recent years. These reports have dealt primarily with leptospiral diseases in which the etiologic agents were the *Leptospira icterohaemorrhagiae*[1, 5] and, to a lesser extent, *Lept. canicola*,[6, 9] *Lept. pomona*,[10, 13] and outbreaks of *Lept. autumnalis* in troops.[14, 15]

To our knowledge there have been only two cases of leptospirosis due to *Leptospira grippotyphosa* reported in American literature.[16, 17] We are reporting another case, recently seen at Cook County Hospital, Chicago.

CASE REPORT

A 29 year old colored male was admitted to Cook County Hospital on September 8, 1953, with a history of neck pain, calf pain and headache of one week's duration,

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From the Department of Medicine, Cook County Hospital, the Departments of Clinical Science and Medicine, University of Illinois College of Medicine, and the Hektoen Institute for Medical Research, Chicago, Illinois.

vomiting for four days, and anorexia for one day. The patient stated that about one week before admission he noticed an intermittent severe pain in the nape of his neck which radiated to the back of his head, and was of a pressing nature, sometimes throbbing, not relieved by aspirin and lasting about two hours. At the same time he noticed severe shooting pains in his calves and thighs, especially upon standing or walking. About three days before admission he noticed a constant dull ache in his neck and calf muscles. He stated that he had vomited two or three times daily five days prior to admission. Vomiting occurred when the headache was most severe, and relieved the severity of the headache. The vomitus was composed of only food contents. For the past week he had been excessively tired and enervated and had slept much more than usual. He had never been jaundiced and had not noticed that his eyes were yellow. He stated that his urine was dark for three days before admission, but he had not noticed the color of his stools. For 24 hours before admission he had had anorexia for all food.

Previous medical and family histories were negative. Systemic review disclosed nothing abnormal. The patient was born in Chicago and had lived there all his life, except for annual trips to Kentucky up to eight years ago. In Chicago he had lived in a six room apartment with his wife, father and five children for the last two and a half years. He and his wife shared a single room. During the summer months the patient and his family frequently picnicked in the Chicago Park District and Forest Preserve and swam in the park lakes.

Physical examination revealed a well developed, well nourished colored male in no distress. Blood pressure was 120/80 mm. of Hg; pulse, 80 and regular; respiratory rate, 16; temperature, 98.6° F. Except for some tenderness to deep palpation in the right upper quadrant, there were no abnormalities on physical examination. Urinalysis revealed a dark urine: specific gravity, 1.030; albumin, 1 plus; bilirubin, 4 plus; negative for urobilinogen. Hemogram showed a hemoglobin of 100 per cent, white blood cells 5,400, and normal platelets. Differential count showed 55 per cent neutrophil polymorphonuclears, 3 per cent neutrophil bands, 2 per cent eosinophils, 28 per cent lymphocytes and 10 per cent monocytes. The heart and lungs were normal on x-ray. Heterophil agglutination was positive, 1:28. Agglutinations for typhoid, brucella and salmonella were negative. Blood cultures were negative. The electrocardiograph was normal. On September 8 total serum proteins were 7.1 gm. per 100 c.c.; serum cholesterol, 188 mg. per 100 c.c.; serum alkaline phosphatase, 5.1 Bodansky units per 100 c.c.; icterus index, 22 units; cephalin flocculation test, 2 plus; thymol turbidity, 7 units; gamma globulin, 1.85 gm. per cent. On September 13 blood agglutinations for leptospirosis revealed the following: 1:32 for *Lept. canicola*, 1:32 for *Lept. pomona*, and 1:128 for *Lept. grippotyphosa*. On September 14 the urine was negative for bilirubin and urobilinogen; total serum proteins were 7 gm. per 100 c.c.; serum cholesterol, 178 mg. per 100 c.c.; serum alkaline phosphatase, 8.1 Bodansky units per 100 c.c.; icterus index, 10 units; cephalin flocculation test, 3 plus; thymol turbidity, 7 units; gamma globulin, 1.45 gm. per cent. On September 21 his chemistries were as follows: total serum proteins, 6.7 gm. per 100 c.c.; serum cholesterol, 168 mg. per 100 c.c.; serum alkaline phosphatase, 4.1 Bodansky units per 100 c.c.; icterus index, 8 units; cephalin flocculation test, 4 plus; thymol turbidity, 7.9 units; gamma globulin, 1.7 gm. per cent. The clinical course in the hospital was entirely uneventful. Antibiotics were not used. The patient made a complete recovery and was discharged from the hospital on September 22, 1953. He was seen subsequently at clinic; he had no complaints and felt perfectly well. On November 11, 1953, agglutinations for leptospirosis were repeated and were found entirely negative for *Lept. canicola*, *Lept. pomona* and *Lept. grippotyphosa*.

Discussion

The causative organism of the clinical entity of *Lept. grippotyphosa* was first isolated by Tarasoff in 1928, and it was he who named it so because the symptomatology of this disease resembled that of typhoid fever.[18] Disease caused by *Lept. grippotyphosa* has been designated by many names, including mud fever, harvest fever, swamp fever, slime fever, August fever, field fever, water fever and, in Europe, schlammfieber. Man is infected by contact with mud or water contaminated with the urine of animal carriers. In Europe known animal reservoirs are field and bank voles and wood mice. In this country animal reservoirs have not yet been discovered.[19] The incubation period of *Lept. grippotyphosa* is approximately two to 10 days, and is usually followed by symptoms which closely resemble a mild attack of Weil's disease but with the meningeal signs more prominent than jaundice. In this respect it is similar to canicola fever. The disease is frequently ushered in by a sudden onset of headache, fever, chills and pains in the back, neck and limbs. Gastrointestinal symptoms of nausea, vomiting and diarrhea are often present. Renal involvement, conjunctivitis and inguinal adenitis not uncommonly occur. A morbilliform rash over the face and body is occasionally seen. The disease usually runs a benign course, with a mild declining fever lasting approximately one week. There is sometimes a febrile relapse with exacerbation of symptoms after this period. Fatal cases are very rare, a mortality rate of 0.4 per cent having been reported.[20]

Laboratory findings depend upon the severity and type of clinical picture present. The more severe cases show a leukocytosis with an increase in polymorphonuclear leukocytes. The sedimentation rate is usually elevated. Cases with renal involvement show a mild azotemia, albuminuria, and red cells and casts in the urine. Hepatic involvement, when present, is usually mild. Cases showing meningeal involvement reveal a mild pleocytosis (20 to 300 cells), predominantly of the lymphocyte variety.

Laboratory confirmation of the diagnosis depends on isolation of the causative organism, either directly or by blood culture, or on specific agglutination tests.[1, 21, 22] The initial rise in antibody titer may occur as early as the seventh day of the disease, and reaches a maximum between the second and third weeks. Direct blood culture technics and serologic complement fixation using sonic-vibrated leptospiral antigens have been used successfully in establishing a diagnosis.[21, 22] In contrast to the agglutination tests, the latter method is simple and may in time become available for use even in smaller hospitals. Antibiotic therapy has not been established as a useful therapeutic agent in leptospiral infections.[22]

The clinical symptoms, laboratory findings and course in our patient are compatible with a mild case of *Lept. grippotyphosa*, the mild degree of illness probably accounting for the absence of certain of the clinical and laboratory findings previously described. The patient probably contracted the disease while bathing in the outlying park lakes, which may have been contaminated by animal excreta containing the *Lept. grippotyphosa*. Because of the mild nature of the symptoms of *Lept. grippotyphosa*, Spain and Howard have pointed out that the disease may easily "escape recognition and be diagnosed as infectious hepatitis, or fever of unknown origin."[16] Both their case and ours presented a picture much more in keeping with infectious hepatitis than with Weil's disease.

Jaundice and evidence of parenchymal liver damage, which are described as uncommon in the European literature, were present in both cases. Both gave histories of one week's duration, with an uneventful hospital convalescence of about three weeks' duration. Our case showed neck pain and headache, which is not common in infectious hepatitis but is characteristic of leptospirosis. Bigham's case [17] of benign aseptic meningitis due to *Lept. grippotyphosa* presented a picture much more in keeping with the disease as described in the European literature [20, 24] and did not have jaundice.

There are about 20 antigenically specific strains of leptospira known, of which at least six, including *Lept. icterohaemorrhagiae, Lept. canicola, Lept. pomona, Lept. autumnalis, Lept. bataviae,* and *Lept. grippotyphosa,* have been described as occurring in the United States.[5] Not only may the clinical picture vary with the particular strain responsible for the disease, but different clinical syndromes may also appear in the disease entity caused by the same strain, and similarities as well as differences are gradually becoming apparent as more cases are being diagnosed and reported in the literature. It is quite apparent now that leptospirosis is not a rare disease in the United States despite the fact that "current knowledge of leptospirosis in the United States today is extremely limited," [1] and many more cases will be uncovered as physicians become more aware of its symptoms and as better laboratory facilities are provided. In recent years it has been shown that leptospirosis due to *Lept. icterohaemorrhagiae, Lept. canicola* and *Lept. pomona* is not uncommon in this country. This will probably prove true for *Lept. grippotyphosa* as well.

Summary

1. A case of leptospirosis due to *Lept. grippotyphosa* is presented.

2. The variety of clinical symptoms produced by this particular strain of leptospira is discussed.

3. A greater index of suspicion by the physician, an appreciation of the varied symptomatology, and an increased availability of confirmatory diagnostic laboratory procedures will undoubtedly reveal an increasing incidence of this disease in the United States.

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EDITORIAL

CERTAIN TRENDS IN UNDERGRADUATE MEDICAL EDUCATION

For twenty years at least the medical curriculum has been in a state of upheaval. Trends that first appeared at the beginning of the century are being opposed by contrary trends, and in some instances educational practices long since abandoned are being revived in new form. In addition to the changes in undergraduate medical education there has been a tremendous expansion in postgraduate and graduate education, but this is not our subject. The alterations in the undergraduate course are in part the outcome of attempts to include in the curriculum the many additions that have been made to specialized knowledge. In part the change consists of the great expansion of the instruction in psychiatry, and in part to the place now taken in the curriculum by what we may call community or social medicine.

If one wishes to schematize the events in undergraduate medical education in the last half-century it might be done as follows: Before, and more rapidly after, the Flexner report in 1910, medical schools, especially those affiliated with and integrated in universities, tended for many years to withdraw from the medical life of their communities, to develop an absorption in medical research, to be interested chiefly in organic disease, and to stress the development of specialists.

Prior to 1910 the faculties of medical schools were composed chiefly of medical practitioners, exception being made of a relatively small number of full-time teachers of the medical sciences. Along with its major defects this system had one quality of value. The clinical chairs were held in the better schools by the leading practitioners and consultants of the community. These men brought to their teaching a point of view developed by their experience with disease in the home, the office and the hospital. They were accustomed to take into account the family and the environment. They were also very commonly the leaders in the medical activities of the profession in their community.

The period of the withdrawal of medical faculties from the medical life of the community was observable particularly in those schools which had recently gone over more or less completely to the "full-time" systems. Appointments under this system were usually based chiefly on the record of the physician in laboratory or clinical research, and it was the development of fruitful research in the school that was expected of such appointees. Only occasionally did such faculty members develop an interest in the relation of the school to the community.

In the earlier years of the century medical investigation was chiefly centered on the infectious diseases. Later, as biochemical and physiologic methods were developed, research in metabolic, endocrinologic, cardiovascular, respiratory, hematologic, gastrointestinal and neoplastic disease

increased rapidly. These investigations dealt almost exclusively with organic disease. Certain physiologists—notably Richet and later Cannon —made valuable contributions to our understanding of the mechanisms involved in the somatic symptomatology of the emotions; but by and large, through the first quarter-century there was little interest shown in the schools in what were called functional disorders, and still less in mental disease.

This absorption in organic disease led, in the clinical field, to specialization. All the major clinical departments in the schools began the development, which still continues, of numerous subdepartments, divisions and sections staffed by specialists and aspirants to specialization. Such clinical specialization yielded the values inherent in a large experience in a narrow field and in the skills peculiar to that field. Less frequently have the clinical specialties advanced knowledge of basic causes, mechanisms and interrelationships.

The concerted attack on organic disease in the last half-century has led to dramatic results. The knowledge gained of the microbiology and the epidemiology of the infectious diseases, supplemented later by the discoveries of specific remedies, has been applied by the health departments and the medical practitioners to such effect that mortality rates from this group of diseases have dropped to a very subordinate position in the list of the chief causes of death. We are only beginning to realize the tremendous impact these medical victories have had upon the composition of our population and thereby upon family, industrial and state socio-economic problems.

The brilliance of successes obtained as a result of scientific research tended for a long time to blind medical educators to the fact that, in the training of a physician for the practice of medicine, more was required than knowledge of basic medical sciences and an adequate acquaintance with the organic diseases. The preoccupations of the faculty with medical research were apt to produce limitations in the breadth of interest of the students. Frequently the medical student of those days developed very little insight into what illness did to the patient as a human individual or to his family. He was accustomed to seeing little interest shown in the effects of stress and anxiety upon the bodily functions. In an era in which preventive medicine was making such great contributions to the health of the people, the courses given in the schools in public health were notoriously unpopular with the students. It came to be realized that the teaching of medicine in the schools with dominant interests in research left the student with a faulty appreciation of the scope of medicine, of the complexity of the medico-social problems he would meet in practice, and of the nature and organization of the medical world outside the school of medicine.

A development in the medical curriculum which has tended to counteract the purely scientific interests of the faculties has been the appearance, especially in the last thirty years, of systematic psychiatric undergraduate in-

struction. Psychiatry within this period has become a major feature in American life and in American medicine. From one point of view its present success is a measure of the degree to which the physicians of the more purely scientific era of medical education had failed to meet needs in their professional relationships with patients. The patient suffering with disease feels the need of friendly interest and understanding; and, even more, the patient with alarming symptoms not explained by manifest disease is dependent on his physician for explanation and reassurance. These needs have always been a determinant in the relationship between patient and physician. They have always been sensed and met in one way or another by successful family physicians. It has been the major achievement of psychiatry in medical education to reëmphasize this basic function of the good physician, and to help the student gain experience in the approach to this aspect of his patient's situation. Some question arises whether, in the flush of their successful invasion of the curriculum, the psychiatric faculty have not seized more time than they can use to good advantage. They are indeed aggressive partners in medical education. The natural expansion of their philosophy leads them from the individual to the family and then to the environmental influences upon family life, and so to the community. Thus they ally themselves with the social scientists and with the clinical home care program. With equal facility they descend from the adult individual through the child to the fetus and join with the geneticist, the neuro-anatomist, the neurophysiologist and the psychologist in tracing growth and development of the personality.

These multiple interests and contacts of psychiatry in medical eduction are still for the most part not clearly formulated or accepted, but in the pioneer phase this type of psychiatric instruction is stimulating. How nutritious it really is remains to be determined.

The medical curriculum, long after psychiatry had won a secure position, still continued to fail to acquaint its students with the great changes that were occurring in the applications of medical knowledge in the community. Striking increases have occurred in the last quarter century in the organized medical activities unconnected with schools of medicine. It is significant that in many of these, lay people play a dominant rôle. The demonstration of the possibilities of medicine afforded by the conquest of many heretofore dread diseases produced a fundamental change in the reaction of our population, from one of acceptance of death from disease as an unavoidable disaster to one of demand for a cure of all diseases.

Since it was preventive medicine in departments of health which applied successfully the results of research to the practical control of the major communicable diseases, it is natural that the departments of health—federal, state and local—have been active in newer programs of community-wide health promotion, disease detection and control. Such organized efforts require an administrative body and the coöperation of the practicing physi-

cians and the public. Such teamwork is a striking feature of the medical scene today. The medical care of contagious disease, of the insane, and of the tuberculous has long been in governmental hands. State and city hospitals for chronic disease are increasing in number. Medical care of the indigent in general hospitals is in part financed by taxpayers. More recently, programs for the medical care of the indigent sick in their homes and in doctors' offices are beginning to be undertaken by local or state governments, usually through the medium of the health department.

Aside from this striking expansion of tax-supported medical activities, there has occurred in the last half-century a vast proliferation of local and national societies and associations of mixed lay and medical membership which contribute in many important ways to combating specific diseases.

One could enumerate many other features of the complex medico-social milieu into which the young physician will be projected and to which he must adapt himself and whose facilities he must be able to use.

Yet in the majority of medical schools, until the last ten years or so, the medical student received no systematic instruction in the organization of medicine in the United States today, and even less a chance to participate in and evaluate through personal experience organized programs of medical care in the home, mass methods of disease detection, the application of epidemiological methods in the study of community disease problems, or the results that can be obtained in certain disabilities by a well organized program of rehabilitation. Yet it is such programs that are gaining fuller acceptance every year as an essential part of the campaign against disease. In this campaign the public furnishes the demand and the means. The physicians in the coming half-century must either lead the campaign or serve in it under lay leadership.

In the medical schools it has been pediatrics which has shown the way to other clinical departments in combining preventive and curative medicine in their teaching and in their practice. In all schools, within the last ten years especially, there has been great activity in developing more inculcation of the preventive aspects of all diseases, more instruction in community medical resources and how they should be used, and more student participation in medicine outside the hospital. There is pioneering in many varying forms of student responsibility in home care projects. These contacts with the extramural realities of the medical care of a population are having a significant effect on the attitudes of both students and faculty towards community medical problems.

It has been noted that the same half-century which witnessed a great development in medical science was characterized in the medical schools by a restriction of clinical interests to the etiology, pathogenesis, diagnosis and cure of organic disease. Two new trends have helped to restore a broader perspective. The new position of psychiatry in medical education has restored to primacy medical interest in the individual and in the relation of his

social environment, his personality and his emotional reactions to his illness. A rejuvenated course in preventive and community medicine is showing that the possibilities of prevention of the non-communicable diseases are only beginning to be realized—and that outside the school and its hospital lie many of the major medical activities and resources of the community.

These two additions to medical education have done much to make it a better balanced preparation for a medical career.

MAURICE C. PINCOFFS

REVIEWS

Legal Medicine. Edited by R. B. H. GRADWOHL, M.D., Sc.D., F.A.P.H.A., Commander, M.C., U.S.N.R. (Retired). 1093 pages; 17.5 × 25.5 cm. The C. V. Mosby Co., St. Louis, Mo. 1954. Price, $20.00.

Thirty authors have participated in the writing of the 39 chapters that comprise this volume. Dr. Gradwohl has contributed 82 of its 1,051 pages of text.

Although the excellence of certain chapters might justify its acquisition by pathologists, medical examiners, coroners, or others having special interest in the field of legal medicine, the book is not suitable for student use. Its coverage of much of the subject matter is too detailed for the undergraduate law or medical student. Some subject material of importance to the student is either omitted or inadequately presented.

The material presented falls into six categories, as follows: forensic pathology, forensic serology, toxicology, forensic psychiatry, medical jurisprudence, and miscellaneous topics.

Forensic Pathology. The chapter by Regan on authorization for the performance of a medico-legal autopsy contains an excellent summary of the statutes of the various states which define when and by whom an official autopsy may be ordered, but makes no mention of the general legal aspects of voluntary consent for autopsy. The chapters by Newbarr and Myers on the special objectives and technics of the medico-legal autopsy, by Stewart on identification of skeletal remains, by Scott on identification by dental evidence, by Camps on wounds of the head and body, and by Courville on trauma of the central nervous system are excellent. No mention or inadequate presentation of such important subjects as rape, abortion, gun-fire injuries and deaths by conflagration constitute important deficiencies in a book purporting to cover the field of forensic pathology.

Forensic Serology. A chapter by Gradwohl on the identification of blood stains contains a detailed, interesting but not particularly appropriate discussion of the difficulties in distinguishing between the bloods of various species of primates. The chapter would have been improved by a more detailed and critical appraisal of the limitations of such non-specific procedures as the benzidine and phenolphthalein tests. The chapters by Gradwohl and by Schatkin on the medical and legal aspects respectively of blood grouping tests in paternity actions are good. Although the chapter by Gradwohl on the examination of seminal fluid contains a useful description of the acid phosphatase test, it is grossly deficient in dealing with the problem of identifying spermatozoa in the various kinds of stains likely to be presented to forensic pathologists for investigation.

Toxicology. Three chapters, one by Keyes and Goldbaum on poisons and their identification; one by Eisenberg on microcrystallographic procedures for identification of drugs and one by Muehlberger on alcohol, make this one of the strongest sections of the book. The chapter by Freireich on the treatment of poisoning is hardly appropriate for a book on legal medicine.

Forensic Psychiatry. Excellent discussion of important aspects of this subject are contained in the chapters by Satterfield on "Forensic Psychiatry"; by Cady on "Legal Relations of the Mentally Ill"; and by Matthews on "Narcoanalysis for Criminal Interrogation."

Medical Jurisprudence. One chapter consisting of 12 pages of text is devoted to the subject of medical malpractice. Whereas much of the book suffers from

being overwritten, this area is regrettably underwritten. A study of the causes of malpractice actions and of measures to prevent them should constitute a most important part of an undergraduate course in legal medicine.

Miscellaneous Topics. These include chapters dealing with the history of legal medicine, medico-legal problems in workmen's compensation, the examination of hairs and fibers, the expert witness, the medical expert witness, lie detection, police laboratory administration and the legal aspects of trauma and disease.

ALAN R. MORITZ, M.D.

Legal Medicine, Pathology and Toxicology. 2nd Ed. By THOMAS A. GONZALES, M.D., Chief Medical Examiner of the City of New York (Retired); MORGAN VANCE, M.D., Deputy Chief Medical Examiner of the City of New York; MILTON HELPERN, M.D., Chief Medical Examiner of the City of New York; and CHARLES J. UMBERGER, Ph.D., Toxicologist, Office of the Chief Medical Examiner of the City of New York. 1349 pages; 25.5 × 17.5 cm. Appleton-Century-Crofts, Inc. 1954. Price, $22.00.

This second edition of the standard textbook of Legal Medicine properly includes pathology in its title since it is a detailed presentation of the medicolegal aspects of investigating the physical as well as the pathological evidence in a wide variety of sudden and violent deaths. The book is considerably larger than the previous edition which appeared some ten years ago and includes much new subject matter such as the Autopsy Findings in Embalmed Bodies, Direct Injuries of the Heart, Brain Edema from Injuries, Rh-Hr Blood Groups as well as a section on Jurisprudence. The latter half of the book is devoted to the presentation of analytical technics for all substances of medicolegal interest and will serve as a daily manual for analysis as well as a reference book providing information about normal levels of various substances and the significance of elevations of concentrations of these chemicals.

The book is divided into forty-seven chapters and an appendix. The early chapters contain a description of the evolution of the Medical Examiner System in this country, a detailed presentation of the problems of identification, early postmortem changes, the causes of unexpected or sudden natural death and the medical complications of trauma. There are six chapters devoted to blunt injury with numerous illustrations of all varieties. The sections on bullet and other missile wounds are particularly well illustrated. There is a brief section on war gases. The discussion of electrical burns and their characteristics is the most complete available in the American literature. The text on blood groups has been revised by Alexander Wiener and presents up-to-date information on the use of blood grouping and other serological procedures in paternity cases and criminal investigations.

A new chapter on the rights and obligations of physicians, malpractice suits and medicolegal aspects of psychiatry gives excellent coverage to jurisprudence and extends the usefulness of the book. Dr. Umberger in presenting the toxicologic section, has drawn on the cumulative experience of many years and hundreds of thousands of analyses conducted in the Office of the Chief Medical Examiner of the City of New York. Attention is drawn to his unpublished data on putrefacted alcohol and the problem of analysis for alcohol in embalmed bodies.

The format of the book is generally good although in some sections, e.g., the chapter on Sudden and Unexpected Death, the illustrations are many pages away from the text describing the disease under consideration. It is hoped that this can be corrected in subsequent printings.

In summary the book is as complete as any medicolegal text available either in this country or abroad and fills a very essential place in the library of the medicolegal

pathologist, the police investigator, the prosecuting attorney and any others interested in the multiple encounters of medicine and the law in our modern day civilization.

RUSSELL S. FISHER, M.D.

Myokardstoffwechsel und Herztherapie. By Dr. Med. FRITZ PENDL. 248 pages; 24.5 × 17.5 cm. Georg Thieme Verlag, Stuttgart; available in the U. S. A. and Canada from Intercontinental Medical Book Corporation, N. Y. 1954. Price, Ganzleinen DM 29.70.

This monograph attempts to review the known facts and also theories about the functional histology and biochemistry of the myocardium. This is done by condensing numerous scientific papers from the literature. Their selection is liberal but extensive, more for support of views expressed than for the presentation of accepted facts. Still they make for interesting reading. Many opinions and recommendations based upon them are rather provocative, for example, that many hypothetical disturbances of myocardial metabolism occur and may be the cause of heart failure in cited cases of myocardial infarction or other cases of chronic rheumatic heart disease. The description of the management of cardiac decompensation in the illustrative cases should be corrected in a future edition. It appears inadequate, haphazard and hardly the result of sound clinical judgment. His statement that MAP (muscle adenosine phosphoric acid) and other similar organic extracts or concoctions are beneficial to myocardial metabolism are outdated by many years. The recommendation that adrenal cortical extracts are better than strophanthin, digitalis or mercurial diuretics for heart failure should not be followed. This particularly after the suggestion that liver extracts are good for the distress of a congested liver. A study and perusal of present day knowledge and concepts in electrolyte disturbances of congestive heart failure would have modified many opinions expressed.

The book gives proof to the studious accumulation of facts from the library and with the flame photometer. Many of the opinions and recommendations are interesting but should not be followed.

The printing and reproduction of illustrations are excellent.

A. G.

Diseases of the Skin. 8th Ed. By OLIVER S. ORMSBY, M.D., Late Rush Professor of Dermatology, University of Illinois; Attending Dermatologist to the Presbyterian Hospital of Chicago; and HAMILTON MONTGOMERY, M.D., M.S., Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. 1503 pages; 16 × 25.5 cm. Lea & Febiger, Philadelphia. 1954. Price, $22.00.

This edition is an up-to-date, all inclusive text on dermatology. It is probably the best of its kind published in English. As in previous editions, the morphologic pictures of the various skin lesions are clearly described and the relationship of these conditions to system dysfunctions is stressed in each case. With each entity there is an excellent summary dealing with the etiology, pathology, differential diagnosis and accepted modes of treatment. Both clinical and histopathological photographs are excellent in every detail. In this new text the newer methods of therapy including the use of the antibiotics and steroids are carefully discussed. New chapters have been included dealing with the cutaneous vascular diseases, and chemistry and physiology of the skin, and mycology.

This book will prove of inestimable value to the student in dermatology, general practitioner, dermatologist and internist. This reviewer is enthusiastic in making such a recommendation.

H. M. R., JR.

The Management of Pain, with Special Emphasis on the Use of Analgesic Block in Diagnosis, Prognosis and Therapy. By JOHN J. BONICA, M.D., Director, Department of Anesthesia, Tacoma General and Pierce County Hospitals. 1533 pages; 18.5 × 26.5 cm. Lea & Febiger, Philadelphia. 1953. Price, $20.00.

Considering that the most frequent complaint of patients presenting themselves to physicians is pain, and that the control of pain can be the most vexing problem facing a practitioner, this book is an earnest attempt to gather in one volume a practical and workable approach to the control of pain and painful states. The book presents the accumulated experience, all the presently available studies and the technics in current use in the control of pain. It is divided into three major sections.

The first section is a detailed investigation into the nature of pain. This difficult task is approached from an anatomical, physiological and psychological standpoint with a presentation of the experience gained in the laboratory. The author emphasized that such experimental data, while extremely valuable, cannot be transferred directly to clinical conditions because an artificial separation of pain perception and pain reaction does not exist clinically. Classification of such an elusive subject of necessity must be arbitrary but the author presents a reasonably consistent classification of types of pain seen in the patient. At the end of this section is a review of the effects of pain on the physiologic and psychologic functions of the body which should be recommended reading for all physicians.

The second section of the book is devoted to technics in current use to control pain and painful conditions. Although there are good reviews of the use of analgesic drugs, roentgen therapy, physiotherapy, psychologic and neurosurgical management in the treatment of pain, the bulk of this section is devoted to the use of analgesic nerve block in the diagnosis, prognosis and therapy of painful states. The author, an anesthesiologist, utilizing his wealth of experience in this field, writes this section with loving care and evidences his intense interest in this aspect of pain control. Technic-wise this section is excellent with commendable emphasis being placed on radiographic control in nerve blocking.

The final section of the book is a detailed discussion of specific painful syndromes and pain producing diseases and the various approaches to the alleviation of pain and return of function in each condition. The proper evaluation and handling of each problem are discussed and a suggested program of management given.

This book is well written and answers a long felt need in one of the most neglected fields of medical practice. It is recommended reading for all anesthesiologists and all physicians who are especially interested in initiating or maintaining a "pain" clinic or service. It will be useful to most practitioners as a reference book.

P. R. H.

An Atlas of Pelvic Operations. By LANGDON PARSONS, M.D., Professor of Gynecology, Boston University School of Medicine; and HOWARD ULFELDER, M.D., Assistant Clinical Professor of Gynecology, Harvard Medical School. Illustrated by MILDRED B. CODDING, A.B., M.A. 231 pages; 29.5 × 36 cm. W. B. Saunders Company, Philadelphia. 1953. Price, $18.00.

This work is primarily an atlas presenting the usual gynecological operations. However, it also includes a pictorial description of operative procedures in other closely allied fields, such as surgery of the intestinal tract, reparative technic used in hernial defects, urological problems confined to the lower tract, and a miscellaneous group including minor operations, i.e., repair of fistulae, vein ligation, dehiscence and resuture. The final section is devoted to operation for malignant disease so well developed by Joe Vincent Meigs, to whom this work is dedicated by his co-workers.

The illustrations, done by Mildred B. Codding, are of the line type and readily

portray the various steps of the operative procedures. The drawings are plentiful in number, are concise and the continuity of the various operations is easily understandable.

The dimensions of the atlas (11.5 by 14.5 inches) make for awkward handling. However, this format may have been necessary to accommodate the context which is as follows: adjacent to the binding a column devoted to operative description is present which well explains the various drawings in chronological order and the various steps are clearly unfolded.

One concludes from a survey of the operative procedures that in general the subject is completely presented. However, the reviewer believes that a number of valuable procedures and technics have been omitted from the discussion.

In conclusion, the reviewer feels that this work is most carefully executed, is readily understandable and should be highly recommended to gynecologists and surgeons. It will be of great aid to the surgical house officer during his course of training where special gynecological instruction is limited.

A study of this atlas will also be most helpful to the general surgeon who feels that he is inadequately trained in pelvic surgery. One hopes, however, that those not well conversant with surgical procedures will not be tempted past their bounds of ability and undertake the more radical operations which appear pictorially rather simple.

J. M. H., Jr.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Biology of Anopheles gambiae: *Research in French West Africa. World Health Organization Monograph Series No. 9.* By M. H. Holstein, Dr. ès Sc. 172 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $2.00.

Cancer of the Thyroid: A Monograph for the Physician. Ninth of a Series on the Early Recognition of Cancer. By John deJ. Pemerton, M.D., Emeritus Member, Section of Surgery, and B. Marden Black, M.D., Section of Surgery, Mayo Clinic, Rochester, Minnesota. 46 pages; 24 × 16 cm. (paper-bound). 1954. American Cancer Society, Inc., New York. Price, free.

Color Atlas of Pathology: Endocrine System, Including Pituitary, Thyroid, Parathyroid, Adrenals and Pancreas; Gynecology and Obstetrics, Including Reproductive Organs; Breasts; Male Genital Tract; Skin. Vol. II. Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. 450 pages (1,032 figures in color on 343 plates); 25 × 18.5 cm. 1954. J. B. Lippincott Company, Philadelphia. Price, $20.00.

Diseases of the Skin, for Practitioners and Students. 4th Ed. By George Clinton Andrews, M.D., F.A.C.P., Clinical Professor of Dermatology, College of Physicians and Surgeons, Columbia University, etc. 877 pages; 25.5 × 17 cm. 1954. W. B. Saunders Company, Philadelphia. Price, $13.00.

Myocardial Infarction, Its Clinical Manifestations and Treatment with Anticoagulants: A Study of 1031 Cases. This is a Report of the Committee on Anticoagulants, Created by the American Heart Association, and Reflects that Committee's Findings in the Matter Under Study. By Irving S. Wright, M.D., Charles D.

MARPLE, M.D., and DOROTHY FAHS BECK, Ph.D. 656 pages; 26 × 17.5 cm. 1954. Published for The American Heart Association by Grune & Stratton, New York. Price, $8.50.

The Pineal Gland: A Review of the Physiologic Literature. By JULIAN I. KITAY and MARK D. ALTSCHULE. 280 pages; 22 × 14.5 cm. 1954. Published for the Commonwealth Fund by Harvard University Press, Cambridge. Price, $5.00.

A Practical Manual of Diseases of the Chest. 4th Ed. By MAURICE DAVIDSON, M.A., M.D., Oxon., F.R.C.P. Lond., Consulting Physician to the Brompton Hospital for Consumption and Diseases of the Chest, etc.; with the assistance of JOHN H. FRIEND, M.D. Lond., M.R.C.P. Lond., Saltwell Research Scholar, Royal College of Physicians, etc. 647 pages; 25 × 17 cm. 1954. Oxford University Press, New York. Price, $19.25.

Proceedings of the First World Conference on Medical Education, London, 1953, Held Under the Auspices of the World Medical Association. 804 pages; 25 × 16 cm. 1954. Oxford University Press, New York. Price, $16.00.

The Psychological Variables in Human Cancer: A Symposium Presented at the Veterans Administration Hospital, Long Beach, California, October 23, 1953. Edited by JOSEPH A. GENGERELLI, Professor of Psychology, University of California at Los Angeles, and FRANK J. KIRKNER, Chief Clinical Psychologist, Veterans Administration Hospital, Long Beach, California, etc. 135 pages; 22 × 14.5 cm. 1954. University of California Press, Berkeley. Price, $3.00.

Rheumatic Fever (DM: Disease-A-Month Series, Monthly Clinical Monographs on Current Medical Problems). By LOWELL A. RANTZ. 35 pages; 20 × 13.5 cm. (paper-bound). 1954. The Year Book Publishers, Inc., Chicago. Price, $9.00 postpaid for 12 monthly issues.

Staube, Gase, Dämpfe. Verhandlungen der Deutschen Gesellschaft für Arbeitsschutz. Band 2. By DR. MED. HANS LOSKANT and DR. MED. EDWART MAGER. 280 pages; 23 × 15.5 cm. (paper-bound). 1954. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, DM 25.–

Die Staublungenerkrankungen. Band 2. By o. ö. PROF. DR. MED. K. W. JÖTTEN, DR. MED. W. KLOSTERKÖTTER and PRIV.-DOZ. DR. RER. NAT. G. PFEFFERKORN. 424 pages; 21 × 15 cm. (paper-bound). 1954. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, Brosch. DM 40.–, geb. DM 43.–

Surgical Treatment of Cancer of the Cervix. Edited by JOE V. MEIGS, M.D., Clinical Professor of Gynecology, Harvard Medical School, etc. 462 pages; 26 × 17.5 cm. 1954. Grune & Stratton, New York. Price, $12.00.

Urology. Volumes I, II and III. Edited by MEREDITH CAMPBELL, M.S., M.D., F.A.C.S., Emeritus Professor of Urology, New York University; with the collaboration of 51 Contributing Authorities. 2,356 pages (3 volumes); 25.5 × 16 cm. 1954. W. B. Saunders Company, Philadelphia. Price, $60.00 per set.

COLLEGE NEWS NOTES

New Life Member

The College is pleased to announce that Dr. Stephen H. Curtis, of Troy, N. Y., has become a Life Member of the College since the publication of the last list in the November issue of this journal.

Gifts to College Library of Publications by Members

The College is indeed grateful to the following members who have presented copies of their books, in most instances autographed, to the College Library of Publications by Members:

Harry Mandelbaum, M.D., F.A.C.P., Brooklyn, N. Y.—*Ballistocardiography,* with William Dock, M.D., F.A.C.P., and Robert A. Mandelbaum, M.D.

William B. Bean, M.D., F.A.C.P., Iowa City, Iowa—*Monographs in Medicine, Series I,* with Associate Editors Morton Hamburger, M.D., F.A.C.P., John A. Leutscher, Jr., M.D., and Stewart Wolf, M.D., F.A.C.P.

Jack C. Norris, M.D., F.A.C.P., Atlanta, Ga.—*The U.S.S. Bountiful (AH-9) in the Pacific—World War II*

A. J. Kauvar, M.D., F.A.C.P., Denver, Colo.—*Hypoglycemia and the Hypoglycemic Syndrome,* with Martin G. Goldner, M.D., F.A.C.P.

This Library is maintained at College Headquarters, and members frequently present copies of their books to the College; thus, the Library has become a living memorial to the member-authors.

A.C.P. Postgraduate Courses

Spring, 1955, Schedule

DISEASES OF THE BLOOD VESSELS AND THROMBOEMBOLIC CONDITIONS: The New York Hospital, New York, N. Y.; Irving S. Wright, M.D., F.A.C.P., Director. March 14–18, 1955.

PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE: Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, Cleveland, Ohio; A. Carlton Ernstene, M.D., F.A.C.P., Director. March 21–25, 1955.

EARLY DETECTION AND PREVENTION OF DISEASES: University of Pennsylvania School of Medicine, Philadelphia, Pa.; John P. Hubbard, M.D., and Norbert Roberts, M.D., Co-directors. March 28–April 1, 1955.

CLINICAL ELECTROCARDIOGRAPHY: Wayne University College of Medicine, Detroit, Mich.; Gordon B. Myers, M.D., F.A.C.P., Director. April 11–15, 1955.

STRESS AND AGING: The Lankenau Hospital, Philadelphia, Pa.; Edward L. Bortz, M.D., F.A.C.P., Director. April 20–23, 1955. This course will immediately precede the Annual Session of the College at Philadelphia, April 25–29.

SELECTED SUBJECTS IN INTERNAL MEDICINE: Mayo Clinic and Mayo Foundation, Rochester, Minn.; Edgar V. Allen, M.D., F.A.C.P., et al., Director. May 9–13, 1955.

FUNDAMENTAL ADVANCES IN INTERNAL MEDICINE: University of Colorado School of Medicine, Denver, Colo.; Charley J. Smyth, M.D., F.A.C.P., Director; James J. Waring, M.D., M.A.C.P., and Gordon Meiklejohn, M.D., (Associate), Co-directors. June 13–17, 1955.

INTERNAL MEDICINE: University of Cincinnati College of Medicine, Cincinnati, Ohio; M. A. Blankenhorn, M.D., F.A.C.P., Director. Date to be determined.

RHEUMATIC DISEASES: Massachusetts General Hospital, Boston, Mass.; Walter Bauer, M.D., F.A.C.P., Director. Date to be determined.

POSTGRADUATE COURSE

STRESS AND AGING

Sponsored by

THE AMERICAN COLLEGE OF PHYSICIANS

THE LANKENAU HOSPITAL

Lancaster Avenue, West, at City Line
Philadelphia, Pa.

April 20, 21, 22 and 23, 1955

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OFFICERS OF INSTRUCTION

(All of Philadelphia unless otherwise indicated)

BERNARD J. ALPERS, M.D., F.A.C.P., Professor of Neurology, Jefferson Medical College of Philadelphia.

KENNETH E. APPEL, M.D., F.A.C.P., Professor of Psychiatry, University of Pennsylvania School of Medicine.

EDWARD L. BORTZ, M.D., F.A.C.P., Chief of Medicine, Medical Service B, The Lankenau Hospital.

FRANCIS J. BRACELAND, M.D., F.A.C.P., Psychiatrist-in-Chief, Institute of Living, Hartford, Conn.

RICHARD BRICKNER, M.D., Assistant Clinical Professor of Neurology, Columbia University College of Physicians and Surgeons, New York, N. Y.

ERNEST M. BROWN, JR., M.D., (Associate), Assistant Physician, The Lankenau Hospital.

J. S. L. Browne, M.D., F.A.C.P., Professor of Medicine, McGill University Faculty of Medicine, Montreal, Que., Can.

Josef Brozek, Ph.D., Laboratory of Physiological Hygiene, University of Minnesota Medical School, Minneapolis, Minn.

Elmer L. Caveny, M.D., (Associate), Capt., (MC), USN, Head of Neuropsychiatry Section, Bureau of Medicine and Surgery, Washington, D. C.

Earl A. Daugherty, M.D., F.A.C.P., Associate, Medical Service B, The Lankenau Hospital.

David B. Dill, M.D., Scientific Director, Chemical Corps Medical Laboratories, Army Chemical Center, Md.

Joseph T. Freeman, M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.

Joseph T. Hafkenschiel, Jr., M.D., Assistant Physician, The Lankenau Hospital.

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Franz J. Ingelfinger, M.D., Associate Professor of Medicine, Boston University School of Medicine, Boston, Mass.

Chester M. Jones, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School, Boston, Mass.

Richard A. Kern, M.D., F.A.C.P., Professor of Medicine, Temple University School of Medicine; Secretary-General, A.C.P.

Ancel Keys, Ph.D., Director, Laboratory of Physiological Hygiene, University of Minnesota Medical School, Minneapolis, Minn.

Nils P. Larsen, M.D., F.A.C.P., Consulting Internist, Tripler Army Hospital, Honolulu, Hawaii; Governor for Hawaii, A.C.P.

Frederic H. Leavitt, M.D., Assistant Professor of Neurology, University of Pennsylvania School of Medicine.

M. S. Lopusniak, M.D., Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine; Assistant Physician, The Lankenau Hospital.

Olive McCay, Ph.D., Department of Nutrition, Cornell University School of Agriculture, Ithaca, N. Y.

Malcolm W. Miller, M.D., F.A.C.P., Associate Physician, The Lankenau Hospital.

T. Grier Miller, M.D., F.A.C.P., Professor of Medicine, University of Pennsylvania School of Medicine.

E. Sterling Nichol, M.D., F.A.C.P., Director, Miami Heart Institute, Miami, Fla.

Arthur P. Noyes, M.D., Superintendent, Norristown State Hospital, Norristown, Pa.

Nicholas Padis, M.D., Assistant Physician, The Lankenau Hospital.

William L. Peltz, M.D., Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine.

George Morris Piersol, M.D., M.A.C.P., Consultant in Physical Medicine, The Lankenau Hospital; Dean of the University of Pennsylvania Graduate School of Medicine.

Daniel B. Pierson, Jr., M.D., F.A.C.P., Associate Physician, The Lankenau Hospital.

Thomas Pomeroy, M.D., Assistant Physician, Department of Clinical Oncological Research, The Lankenau Hospital.

Stanley P. Reimann, M.D., F.A.C.P., Director, The Lankenau Hospital Research Institute.

Cecelia Riegel, M.D., Research Chemist, The Lankenau Hospital.

Charles Rupp, M.D., Chief, Department of Neuropsychiatry, The Lankenau Hospital.

Joseph J. Rupp, M.D., Assistant Physician, The Lankenau Hospital.

Hans Selye, M.D., Director, Institute of Medicine and Experimental Surgery, University of Montreal Faculty of Medicine, Montreal, Que., Can.

LAUREN H. SMITH, M.D., F.A.C.P., Physician-in-Chief and Administrator, Institute of the Pennsylvania Hospital.

HARRY C. SOLOMON, M.D., Professor of Psychiatry, Harvard Medical School, Boston, Mass.

C. STEPHEN STAHLNECKER, M.D., (Associate), Assistant Physician, The Lankenau Hospital.

JACOB STEKOL, Ph.D., Department of Physiological Chemistry and Nutrition, The Lankenau Hospital Research Institute.

RENDALL R. STRAWBRIDGE, M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.

SIDNEY WEINHOUSE, Ph.D., Department of Metabolic Chemistry, The Lankenau Hospital Research Institute.

EDWARD WEISS, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

JOHN W. WELTY, M.D., Assistant Physician, The Lankenau Hospital.

JOSEPH YASKIN, M.D., Professor of Neurology, University of Pennsylvania Graduate School of Medicine.

WALLACE M. YATER, M.D., F.A.C.P., Director, Yater Clinic, Washington, D. C.; Regent, A.C.P.

SALVADOR ZUBIRAN, M.D., F.A.C.P., Professor of Internal Medicine, Faculty of Medicine and Graduate School of Medicine, National University of Mexico, D. F.

This is a new course on the schedule of the American College of Physicians, emphasizing the effects of stress on the Vascular System, the Digestive Tract, the Nervous System, the Aging Mind, the Chemistry of Growth, and Premature Aging. It will be conducted in a series of symposia and panel discussions. This new field of thought, organized in a correlated course, was conceived by the Director by a faculty well qualified by ability and experience to hold the keen interest of the class. The course is scheduled immediately preceding the 36th Annual Session of the College at Philadelphia, April 25-29, thus making it possible for members from all areas to take the course and attend the Session on one journey.

Symposium I

STRESS AND THE VASCULAR SYSTEM

Moderator

Nils P. Larsen, M.D., F.A.C.P.

The Lankenau Hospital Auditorium

April 20, 1955 Wednesday, 9:00 a.m.

GREETINGS—ORIENTATION

I. The Aging Circulation	Dr. Nils P. Larsen
II. Tension	Dr. Edward Weiss
III. The Chemistry of Vascular Deterioration	Dr. Cecelia Riegel
IV. The Prevention of Occlusions	Dr. E. Sterling Nichol
V. Significant Trends in Research	Dr. Wallace M. Yater

Intermission

Panel Discussion

Symposium II

STRESS AND THE DIGESTIVE TRACT

Moderator

T. Grier Miller, M.D., F.A.C.P.

April 20, 1955 Wednesday, 2:00 p.m.

I. Opening Remarks	Dr. T. Grier Miller
II. Advancing Age and the Digestive Tract	Dr. Chester M. Jones
III. Emotions and Digestion	Dr. William L. Peltz
IV. The Ulcer Problem	Dr. Salvador Zubiran
V. The Aging Colon	Dr. M. S. Lopusniak
VI. Significant Trends in Research	Dr. Franz J. Ingelfinger

Intermission

Panel Discussion

Symposium III

STRESS AND THE NERVOUS SYSTEM

Moderator

Frederic H. Leavitt, M.D.

The Lankenau Hospital Auditorium

April 21, 1955 Thursday, 9:00 a.m.

I. The Aging Nervous System	Dr. Frederic H. Leavitt
II. Stress and Physiological Aging; Heredo-Degenerative Disorders	Dr. Harry C. Solomon
III. Stress and Physiological Aging; the Muscular Dystrophies and Atrophies	Dr. Bernard J. Alpers
IV. Stress and Physiological Aging; the Demyelinating Diseases, Especially Multiple Sclerosis	Dr. Richard Brickner
V. Trends in Research of the Aging Nervous System	Dr. Charles Rupp

Intermission

Panel Discussion

Symposium IV

THE AGING MIND

Moderator

Lauren H. Smith, M.D., F.A.C.P.

April 21, 1955 Thursday, 2:00 p.m.

I. Psychiatry, Stress and Aging	Dr. Lauren H. Smith
II. Stress and the Psychoneuroses	Dr. Joseph C. Yaskin
III. Stress and the Functional Psychoses	Dr. Francis J. Braceland

IV. Stress and the Organic Psychoses	Dr. Joseph F. Hughes
V. Mental Deterioration in the Pre-Senile Period	Dr. Arthur P. Noyes
VI. Anti-Stress Factors in the Elderly	Dr. Kenneth Appel

Intermission

Panel Discussion

Symposium V

THE CHEMISTRY OF GROWTH

Moderator

Stanley P. Reimann, M.D., F.A.C.P.

The Lankenau Hospital Auditorium

April 22, 1955 Friday, 9:00 a.m.

I. The Composition of the Body	Dr. Ancel Keys
II. Hormonal Targets	Dr. Sidney Weinhouse
III. Protein Synthesis and Aging	Dr. Jacob Stekol
IV. Nutrition and Longevity	Dr. Olive McCay
V. The Nature of Fatigue	Dr. David B. Dill

Intermission

Panel Discussion

Symposium VI

STRESS AND PREMATURE AGING

Moderator

Richard A. Kern, M.D., F.A.C.P.

April 22, 1955 Friday, 2:00 p.m.

I. Skeletal Aging	Dr. Joseph T. Freeman
II. Stress and Cancer	Dr. Thomas Pomeroy
III. Stress and the Endocrine System	Dr. J. S. L. Browne
IV. Stress and Premature Aging	Dr. Hans Selye

Intermission

Panel Discussion

ANTI-STRESS EVENING

Bellevue-Stratford Hotel

The Rose Garden

Friday, April 22, 1955

6:30 p.m. Experiments with Anti-Aging Factors	Group Participation
7:15 p.m. Dinner	
9:00 p.m. Introduction of Distinguished Guests	
"Hawaiian Folklore"	Dr. Nils P. Larsen

Symposium VII

STRESS AND AGING

Moderator

George Morris Piersol, M.D., M.A.C.P.

The Lankenau Hospital Auditorium

April 23, 1955 Saturday, 9:00 a.m.

Panel Discussion

Dr. J. S. L. Browne	Dr. T. Grier Miller
Dr. Richard A. Kern	Dr. Stanley P. Reimann
Dr. Nils P. Larsen	Dr. Hans Selye
Dr. Frederic H. Leavitt	Dr. Lauren H. Smith

Intermission

10:40 a.m. Physical Fitness and National Security	Dr. Elmer L. Caveny
11:00 a.m. Human Performance and Aging	Dr. Josef Brozek
11:30 a.m. Aging and Growth Potentials	Dr. Edward L. Bortz

A.C.P. REGIONAL MEETINGS RECENTLY HELD

ARKANSAS-OKLAHOMA Regional Meeting, Oklahoma City, Okla., October 8–9, 1954:

This Regional Meeting was held in conjunction with the A.C.P. Postgraduate Course "Selected Problems in Internal Medicine." Dr. Marion A. Blankenhorn, First Vice President of the College, represented the Regents and Officers of the College and gave a paper on the scientific program, as well as acting as the chief speaker at the evening banquet. The registration indicated an attendance of 65 members and 39 guests; total, 104.

MIDWEST Regional Meeting, Indianapolis, Ind., October 9, 1954:

This meeting covered the States of Illinois, Indiana, Iowa, Minnesota and Wisconsin. The attendance record was as follows:

	Ill.	Indiana	Iowa	Minn.	Wis.	Totals
Fellows	36	42	2	2	7	89
Associates	22	26	1	—	9	58
Non-Members	31	71	2	3	—	107
Totals	89	139	5	5	16	254

Among the special guests were Cyrus C. Sturgis, M.D., President, Philip S. Hench, M.D., Regent, Walter L. Palmer, M.D., Regent, and Karver L. Puestow, Regent. The scientific program covered two days' session and included twenty formal papers and a Clinical-Pathological Conference. Madison, Wis., was chosen as the site of the 1955 Regional Meeting, with Drs. Karver L. Puestow, Regent, of Madison, and Frederick W. Madison, of Milwaukee, Governor for Wisconsin, in charge.

SOUTHEASTERN Regional Meeting, Edgewater Park, Miss., October 15–16, 1954:

The Southeastern Regional Meeting was expanded this year to include not only Alabama, Florida, Georgia, South Carolina and Cuba, but also Mississippi and Louisiana. There were in attendance 92 members and 38 guests; total, 130, the largest registration coming from Louisiana, Alabama and Mississippi. Dr. William D. Stroud, Treasurer of the College, was scheduled to be the official guest from the Officers and Regents of the College, but due to the hurricane Hazel, his plane was grounded and he was unable to reach the meeting. One of the features on the program was the showing of a kinescope film of the College telecast of September 23 on "The Management of Hypertension." The showing of the film was well received; the scientific program was of high quality, and the meeting a definitely successful one.

KENTUCKY Regional Meeting, Lexington, Ky., October 16, 1954:

While the program was an excellent one, the attendance was smaller than the Kentucky Regional Meeting when held in Louisville, the total attendance consisting of 31 members and 15 guests; total, 46. Dr. Wallace M. Yater, Regent, Washington, D. C., was the guest of honor, representing the Officers and Regents of the College and was the chief speaker at the banquet.

NEW MEXICO Regional Meeting, Albuquerque, N. M., October 20, 1954:

The exceptionally fine program had been prepared during the summer by the late Dr. Walter I. Werner, Governor for New Mexico. Dr. Werner lost his life in an airplane crash in August. Dr. H. L. January (Associate), of Albuquerque, carried on during the interim, until Dr. Robert Friedenberg, of Albuquerque, was officially appointed interim Governor for New Mexico until the next regular election. Dr. Philip S. Hench, Regent, Rochester, Minn., was the speaker and official representative of the Officers and Regents at the banquet meeting. The attendance consisted of 14 members and 35 guests; total, 49. There are only 19 College members in New Mexico; hence, the percentage of member attendance was excellent. A special feature of the banquet was an illustrated lecture by Dr. Frank C. Hibben, Director, Department of Anthropology, University of New Mexico; his title, "Mystery of the Stone Towers."

NEW ENGLAND Regional Meeting, Hartford, Conn., October 22, 1954:

The College is particularly gratified with the revival of the New England Regional Meeting, which had been omitted for New England as a whole for the past several years. Dr. John C. Leonard, College Governor for Connecticut, was General Chairman; President Cyrus C. Sturgis and Mr. Edward R. Loveland, Executive Secretary, were special guests who spoke at the banquet. The meeting was characterized by the enthusiastic support and endorsement of all members in attendance. The final registration figures have not been recorded with the Executive Offices, but there was a total of some 350 members and guests. Great credit is due to Governor Leonard and the local Committees, both for the scientific and social aspects of the meeting.

WESTERN PENNSYLVANIA Regional Meeting, Pittsburgh, Pa., October 27, 1954:

This Regional Meeting was held in connection with an A.C.P. Postgraduate Course, "Selected Subjects in Internal Medicine," conducted at the University of Pittsburgh, October 25–30, under the Directorship of Dr. R. R. Snowden and the Co-Directorship of Dr. Frank J. Gregg. Attendance figures are not yet available, but it is estimated that there were about 125 present at the banquet in the evening. Following an address at the banquet by the Executive Secretary, Mr. Edward R. Loveland, the Western Pennsylvania members presented to Mr. Loveland a very

beautiful clock, with suitable engraving indicating appreciation and affection for his many years of service to the Western Pennsylvania group. Governor C. Howard Marcy unfortunately had been called out of town and Dr. Snowden substituted in his place, except at the banquet, where Dr. Frank J. Gregg acted as Toastmaster. A feature of the banquet was a colored film by Dr. Josiah R. Eisaman, depicting a personal expedition he had made through the Grand Canyon by boat.

Coming Regional Meetings

Before the publication of this item, several Regional Meetings will have been conducted, including the following:

NEW JERSEY Regional Meeting, Newark, N. J., November 3, 1954;
NORTHWEST Regional Meeting, Seattle, Wash., November 4, 1954;
WESTERN NEW YORK Regional Meeting, Syracuse, N. Y., November 19, 1954;
MICHIGAN Regional Meeting, Grand Rapids, Mich., December 4, 1954;
NORTH CAROLINA Regional Meeting, Durham, N. C., December 9, 1954;

Scheduled in the New Year are the following:

OHIO Regional Meeting, Cleveland, Ohio, January 14, 1955:

Dr. Charles A. Doan, Columbus, A.C.P. Governor; Dr. Howard Schwartz, Cleveland, Chairman; special guests, Dr. Marion A. Blankenhorn, First Vice President, Cincinnati; Mr. Edward R. Loveland, Executive Secretary of the College, Philadelphia;

DISTRICT OF COLUMBIA–MARYLAND Regional Meeting, Washington, D. C., January 29, 1955:

Dr. John Minor, Governor for the District of Columbia, Washington, General Chairman; Dr. R. Carmichael Tilghman, Governor for Maryland, Baltimore;

PUERTO RICO Regional Meeting, San Juan, P. R., January 28–29, 1955:

Dr. Rafael Rodriguez-Molina, Governor and General Chairman;

NEBRASKA Regional Meeting, Omaha, Nebr., February 26, 1955:

Dr. Joseph D. McCarthy, Governor, Omaha; special guest from the Board of Regents, Dr. Marion A. Blankenhorn, First Vice President, Cincinnati;

MISSOURI Regional Meeting, Columbia, Mo., February, 1955:

Exact date in February not yet determined. Dr. Carl V. Moore, Governor for Missouri, St. Louis; General Chairman, Dr. W. A. Sodeman, Columbia;

DELAWARE Regional Meeting, Wilmington, Del., February 5, 1955:

Dr. Lemuel C. McGee, Governor for Delaware; Dr. Lewis B. Flinn, Chairman, Wilmington;

ALBERTA, MANITOBA, SASKATCHEWAN Regional Meeting, Regina, Sask., February 5–6, 1955:

Dr. Charles H. A. Walton, Governor for Manitoba and Saskatchewan, Winnipeg, in charge; Dr. D. E. Rodger, General Chairman, Regina;

SOUTHERN CALIFORNIA Regional Meeting, San Diego, Calif., February 12–13, 1955:

Dr. Leland Hawkins, Governor for Southern California, Los Angeles; Dr. Samuel J. McClendon, San Diego, Chairman of Arrangements; Dr. Roy A. Ouer, San Diego, Chairman of the Program Committee; special guests, Dr. George F.

Strong, President-Elect, Vancouver, B.C., and Mr. Edward R. Loveland, Executive Secretary, Philadelphia;

VIRGINIA Regional Meeting, Richmond, Va., February 24, 1955:

Dr. Charles M. Caravati, Governor and Chairman, Richmond; Dr. Cyrus C. Sturgis, President, honored guest;

SOUTHERN ILLINOIS Regional Meeting, Peoria, Ill., March, 1955:

Exact date in March not yet determined. Dr. Charles H. Drenckhahn, Governor, Urbana; Dr. James W. Sours, local Chairman, Peoria;

KANSAS Regional Meeting, Wichita, Kans., March 18, 1955:

Dr. William C. Menninger, Governor, Topeka; Dr. Walter L. Schafer, General Chairman, Wichita.

Report on Evaluation of A.C.P. Postgraduate Television Program

In the immediate preceding issue of this journal, News Note section, appeared the announcement of "An Experiment in Postgraduate Medical Programs by Television." This program on The Management of Hypertension was telecast from New York on September 23, 1954. There were 26 separate outlets extending from coast to coast and including 3 medical conventions. The total number of the audience was 8,494. A questionnaire was distributed to all viewers. The results of the questionnaire are as follows:

1. Was the Telecast worthwhile to you?
   Yes, 1,159 No, 11
2. Was the performance dignified and up to the standards of the A.C.P.?
   Yes, 1,151 No, 19
3. Would you be in favor of an open-circuit telecast of the same subject?
   Yes, 361 No, 690

It will be noted that the number who returned questionnaires up to October 21 was 1,170. Those returning questionnaires were given the privilege of submitting titles for further television programs. There were 351 titles submitted for closed-circuit programs; 71 for open-circuit programs. Numerous letters and suggestions were received from various sources, all from men who viewed the program. It is apparent that the program met with almost universal approval and great enthusiasm. Of the limited number of members who did not endorse the program, most of them were unfavorable either because they thought the program could be more inclusive of the field of the management of hypertension or that they did not approve of sponsorship financially by a commercial institution. The figures, of course, disclose a very insignificant number of negative votes. It is apparent that about two thirds of those voting were in favor of closed-circuit programs of technical, medical data, believing it would be harmful to the laity to telecast such programs on open circuits.

The Willard O. Thompson Memorial Traveling Scholarship

Following the death of Dr. Willard O. Thompson, F.A.C.P., on March 23, 1954, a movement was initiated among friends of Dr. Thompson to set up, under the administration of the Committee on Fellowships and Awards of the American College of Physicians, a memorial traveling scholarship. The aim of this scholarship, like that of the A. B. Brower Traveling Scholarships, is to provide an opportunity for a worthy young physician, preferably an Associate of the College, to spend a month, more or less, as a visiting fellow at some institution, or institutions, for observation and

postgraduate study. The College Committee can readily facilitate opportunities for this scholarship at outstanding institutions where a month's observation, contact and study will be of exceptional inspiration and a practical source of training.

Many of Dr. Thompson's former patients have already made contributions to the fund. It is intended to build up a fund of $10,000.00, which will perpetually endow this Traveling Scholarship. Physician friends and former students of Dr. Thompson have expressed a desire to make contributions to the fund in honor and memory of Dr. Thompson. Dr. Phebe K. Thompson, 1430 Lake Shore Dr., Chicago 10, Ill., is acting as Treasurer and remittances may be sent to her. She in turn will officially transmit them to the American College of Physicians.

1955 Essay Contest of the Mississippi Valley Medical Society

The Fifteenth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1955. The Society will offer a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of a general medical interest (including medical economics and education) and of practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States.

The winner will be invited to present his contribution before the 20th Annual Meeting of the Mississippi Valley Medical Society, to be held at the Jefferson Hotel, St. Louis, Mo., Sept. 28–30, 1955, the Society reserving the exclusive right to publish the essay in its official publication, the *Mississippi Valley Medical Journal*. All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5,000 words, and must be received not later than May 1, 1955.

Further details may be secured from Harold Swanberg, M.D., F.A.C.P., Secretary, Mississippi Valley Medical Society, 209–224, W.C.U. Bldg., Quincy, Ill.

Coming Examinations by Certifying Boards

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis.

The written examination will be held Oct. 17, 1955, in major centers throughout the United States and the European and Far East Commands. The final date for filing applications is May 1, 1955.

The following oral examinations have been scheduled:

New Orleans, La.—Feb. 1–4, 1955
Philadelphia, Pa.—May 4–5, 1955
Washington, D. C.—May 6–7, 1955
Portland, Ore.—Sept. 14–16, 1955
Chicago, Ill.—Nov. 30–Dec. 2, 1955.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Written examinations at selected places will be held on Jan. 14, 1955. This is the only written examination which will be given during 1955.

Oral Examinations: New Orleans, La.—March 4–6, 1955
Detroit, Mich.—April 8–10, 1955
New York, N. Y.—June 10–12, 1955
Chicago, Ill.—Oct. 7–9, 1955
Washington, D. C.—Dec. 2–4, 1955.

Dr. William Dameshek, F.A.C.P., was elected President of the International Society of Hematology at the recent Congress meeting attended by over one thousand hematologists, in September, 1954, at Paris. Dr. Dameshek also participated at the Spleen Symposium at Innsbruck, Austria, and at the Third International Congress of Internal Medicine at Stockholm. The Sixth Congress of the International Society of Hematology will be held in Boston in September, 1956.

Dr. Henry J. Tumen, F.A.C.P., was recently appointed Professor of Clinical Gastroenterology in the University of Pennsylvania Graduate School of Medicine.

Dr. George Morris Piersol, M.A.C.P., Philadelphia, Dean of the University of Pennsylvania Graduate School of Medicine, was honored in September when the American Congress of Physical Medicine and Rehabilitation gave him its Gold Key Award for his outstanding contributions to physical medicine.

Dr. Theodore G. Klumpp, F.A.C.P., New York City, has been appointed by former President Herbert Hoover as Chairman of the Task Force on Medical Services of the Hoover Commission on Organization of the Executive Branch of the Government. A member of the Task Force since its formation in 1953, Dr. Klumpp succeeds the late Chauncey McCormick, Chicago, who died in September.

At the Second World Congress of Cardiology, which met in Washington, D. C., in September, Dr. Paul D. White, F.A.C.P., Boston, who served as President of the Congress, was elected President of the International Society of Cardiology, the sponsoring organization of these Congresses. At the same time, Dr. Ignacio Chávez, F.A.C.P., Mexico, D.F., College Governor for Mexico, was elected First Vice President. Other officers include Dr. Louis N. Katz, F.A.C.P., Chicago, Treasurer, and Dr. John H. Palmer, F.A.C.P., Montreal, Assistant Secretary.

Dr. Eugene A. Stead, Jr., F.A.C.P., Durham, N. C., has recently been chosen Vice Chairman of the Scientific Council of the American Heart Association, and Dr. A. Carlton Ernstene, F.A.C.P., Cleveland, has been named Secretary. Dr. Robert L. King, F.A.C.P., Seattle, Wash., automatically became Chairman as the immediate Past President of the American Heart Association. Dr. Howard Wakefield, F.A.C.P., Chicago, College Governor for Northern Illinois, was chosen Chairman of the Subspecialty Board on Cardiovascular Disease of the Council, to serve for a two-year term.

Dr. Daniel E. Jenkins, F.A.C.P., Houston, Tex., was recently elected Vice President of the American Trudeau Society.

Dr. John A. Reisinger, F.A.C.P., Washington, D. C., has been chosen President of the Washington Heart Association.

The New Orleans Graduate Medical Assembly has recently named Dr. Donovan C. Browne, F.A.C.P., its President-Elect.

Dedication ceremonies of the Mayo Memorial, a sixteen-story tower section and three six-story wings connected to present hospital and medical school buildings, were held at the University of Minnesota Medical Center, Minneapolis, Oct. 21–22.

In addition to state and University officials, participating in the ceremonies were Drs. Leonard A. Scheele, F.A.C.P., Washington, D. C., Osborne A. Brines, F.A.C.P., Detroit, Frank H. Krusen, F.A.C.P., and Henry W. Woltman, F.A.C.P., Rochester, Minn., Francis J. Braceland, F.A.C.P., Hartford, Conn., William H. Sebrell, Jr., F.A.C.P., Bethesda, Md., Jack Masur (Associate), Washington, D. C., and other outstanding physicians.

Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., was the principal speaker at the banquet held in conjunction with the sixth Scientific Assembly of the Maryland Academy of General Practice in Baltimore, Oct. 21. Other out-of-state speakers and their topics included Dr. Maurice S. Segal, F.A.C.P., Boston, "Advancements in Therapy of Chronic Pulmonary Emphysema," and Dr. Donald M. Pillsbury, F.A.C.P., Philadelphia, "Dermatology in General Practice."

Dr. Richard J. Bing, F.A.C.P., Birmingham, Ala., Professor of Experimental Medicine and Clinical Physiology at the Medical College of Alabama, gave the Second Harvey Lecture, the Fiftieth Anniversary Series, at the New York Academy of Medicine on Oct. 14. His subject was "The Metabolism of the Heart."

Dr. E. Cowles Andrus, F.A.C.P., Baltimore, Md., President of the American Heart Association, was the guest speaker at the annual meeting and dinner of the Orange County (N. Y.) Heart Association, which met in Port Jervis, Oct. 19.

Dr. Howard D. Fabing (Associate), Cincinnati, President of the American Academy of Neurology, was the guest speaker at the Sixth Western Institute on Epilepsy, held in Galveston, Tex., 22–23. The program was devoted primarily to the psychosomatic aspects of epilepsy.

Dr. Henry J. Tumen, F.A.C.P., Philadelphia, Professor of Clinical Gastroenterology at the University of Pennsylvania Graduate School of Medicine, participated in an annual symposium, "Diseases of the Liver," presented by the Raleigh (N. C.) Academy of Medicine, Oct. 21.

Southern Medical Association Meeting

Under the Presidency of Dr. Alphonse McMahon, F.A.C.P., St. Louis, the Southern Medical Association held its 48th Annual Meeting in St. Louis, Nov. 8–11. Among the speakers and their topics were Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., "The Present Status of Hormonal and Drug Therapy in the Treatment of Ulcerative Colitis"; Dr. E. Hugh Luckey, F.A.C.P., New York City, "Parenteral Fluid Therapy"; Dr. Henry Rappaport, F.A.C.P., Chicago, Ill., "Neoplastic Lesions in Lymph Nodes"; Dr. I. Davidsohn, F.A.C.P., Chicago, "Immunohematologic Aspects of Diseases of Lymph Nodes"; and Dr. E. Harold Hinman, F.A.C.P., San Juan, P. R., "The Public Health and Preventive Medicine in Tropical America."

Immediately preceding the Southern Medical Association Meeting, the American Therapeutic Society held its annual meeting at St. Louis, Nov. 4–6, with Dr. William B. Rawls, F.A.C.P., New York City, as President. His Presidential Address was entitled "Cortisone: A Five-Year Study." Also on the program were Dr. Joseph B. Wolffe, (Associate), Philadelphia, First Vice President of the Society, who spoke on "Atheromatous and Essential Benign Hypertension: Two Clinical Entities—Differential Diagnosis and Treatment," and Dr. Howard Wakefield, F.A.C.P., Chicago, College Governor for Northern Illinois and Treasurer of the Society, who discussed "The Management of Elevated Blood Pressure in Older Women." Dr. Francis M.

Pottenger, Sr., M.A.C.P., Monrovia, Calif., considered "The Correlation of the Physical and Emotional Aspects of Disease," and Dr. William P. Boger, F.A.C.P., Philadelphia, presented "An Evaluation of Oral Penicillin Therapy." Dr. George T. Harrell, Jr., F.A.C.P., Gainesville, Fla., spoke on "Potassium Within the Cells: Therapeutic Implications," and Dr. James F. Gleason, F.A.C.P., Atlantic City, N. J., was a co-author of the paper "Total Gastrectomy." Dr. Kenneth Phillips, F.A.C.P., Miami, Fla., opened the scientific session with a presentation on "Ultrasound Waves in Therapeutics: A Review of the Present Status," and Dr. Edward H. Reinhard (Associate), St. Louis, Mo., gave the Lewis H. Taylor Lecture, "Therapy of the Leukemias and Lymphomas." Also on the program were Dr. Thaddeus D. Labecki (Associate), Jackson, Miss., who told of "The Saga of Lipotropic Therapy," and Drs. G. O. Broun, F.A.C.P., St. Louis, Mo., and J. Winthrop Peabody, Sr., F.A.C.P., Washington, D. C., whose respective subjects were "Phases of Treatment of Hepatic Cirrhosis Other Than Lipotropic Agents" and "Modern Treatment of Pulmonary Tuberculosis."

Dr. L. E. Hines, F.A.C.P., Chicago, and Dr. Darrell C. Crain, Jr., F.A.C.P., Washington, D. C., were among the guest speakers at a scientific assembly sponsored by the Connecticut Academy of General Practice in conjunction with Lederle Laboratories and held in Bridgeport, Oct. 20. Dr. Hines spoke on "The Evaluation of the Newer Drugs in the Treatment of Hypertension," and Dr. Crain on "Local Therapy in the Management of Localized Arthritis, Bursitis and Tendinitis."

Dr. Rudolph H. Kampmeier, F.A.C.P., College Governor for Tennessee, will assume the duties of Editor of the *Southern Medical Journal* as of December 1, 1954, succeeding Dr. M. Y. Dabney, who will retire.

Other important changes have taken place in the administration of the Southern Medical Association. Mr. C. P. Loranz, who for 42 years has been the Executive Officer, the Secretary, Treasurer and General Manager, carrying the title of Secretary-Manager, will retire December 1, 1954, continuing only in an active advisory and public relations capacity. He will be succeeded by two men. Mr. V. O. Foster, formerly Executive Secretary of the Tennessee State Medical Association, will become Executive Secretary and Treasurer, while Mr. Robert F. Butts, formerly an assistant to Mr. Loranz, will become the Business Manager.

Dr. Paul H. Langner, Jr., F.A.C.P., Philadelphia, has been recently appointed Medical Director of the Provident Mutual Life Insurance Company of Philadelphia. With Provident Mutual since 1939, Dr. Langner was made Assistant Medical Director in 1942 and Associate Medical Director in 1948.

Dr. William F. Ashe, Jr., F.A.C.P., has recently been appointed Professor and Chairman of the Department of Preventive Medicine at the Ohio State University College of Medicine, Columbus.

Dr. Edgar P. Copeland, F.A.C.P., Washington, D. C., has resigned as Chief of the Medical Staff at Children's Hospital. Now Chief of Staff Emeritus, Dr. Copeland will continue to be active on the staff.

Dr. G. Watson James, III (Associate), Richmond, Va., has recently been chosen a member of the Council of the American Federation for Clinical Research.

Drs. Barnett Greenhouse, F.A.C.P., New Haven, Conn., George P. Heffner, F.A.C.P., Charleston, W. Va., and William R. Jordan, F.A.C.P., Richmond, Va., have recently been appointed Governors for their respective states by the American Diabetes Association.

Dr. James R. Cook (Associate), formerly on the staff of Cleveland Clinic at Cleveland, Ohio, entered private practice in Orlando, Fla., Oct. 1, 1954, and is a member of the staff of the Orange Memorial Hospital there.

Dr. Joseph C. Doane, F.A.C.P., has recently been made Emeritus Professor of Clinical Medicine at the University of Pennsylvania Graduate School of Medicine, Philadelphia. Promotions at the Graduate School include Dr. Thomas A. Johnson, F.A.C.P., Professor of Clinical Gastroenterology; Dr. Stanley P. Reimann, F.A.C.P., Professor of Oncology; and Dr. Henry J. Tumen, F.A.C.P., Professor of Clinical Gastroenterology. Dr. James L. D. Roth (Associate) has been made Assistant Professor of Gastroenterology.

Dr. J. S. Blumenthal, F.A.C.P., Minneapolis, has been promoted to Clinical Associate Professor of Medicine at the University of Minnesota Medical School and Chief of Allergy Clinic at the University of Minnesota Hospitals in Minneapolis.

As of Oct. 1, Dr. Henry E. Wilson (Associate) was appointed Associate Professor and Vice Chairman of the Department of Medicine at Ohio State University College of Medicine, Columbus. Dr. Wilson was formerly Assistant Professor of Medicine at Northwestern University Medical School.

Capt. Lloyd R. Newhouser, (MC), USN, F.A.C.P., has been placed on the retired list after more than thirty years of active Naval Service. Succeeding him as Director of the Professional Division, Bureau of Medicine and Surgery, Washington, D. C., is Capt. Cecil L. Andrews, (MC), USN, F.A.C.P., who formerly was head of the Bureau's Training Branch. Capt. Newhouser is now Director of the Blood Bank and Associate Director of the Medical Research Foundation of Dade County, Fla.

Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., retired Oct. 1 as Director of the Medical Division of E. I. du Pont de Nemours and Company, but will continue as Associate Medical Director until he retires from the Company, Nov. 1, 1955. Dr. Gehrmann has been with the Company since 1915 and Head of the Medical Division since 1926. At the same time, Dr. C. Anthony D'Alonzo, who was heretofore Assistant to the Manager of the Division, was named Assistant Medical Director.

Dr. James H. Means, F.A.C.P., Boston, Jackson Professor of Medicine, Emeritus, at Harvard Medical School, has recently been appointed Acting Medical Director at the Massachusetts Institute of Technology, Cambridge, where he has been a Consulting Physician for the past three years.

Included among the guest speakers at the series of weekly lectures sponsored by the Hartford (Conn.) Hospital are three Fellows of the College, Drs. Maurice S. Segal and Howard B. Sprague, Boston, and Irving A. Beck, Providence, R. I. The subjects discussed by Dr. Segal and Dr. Sprague on Oct. 30 and Nov. 13 were, respectively, "The Hazards of ACTH Administration in Patients with Pulmonary Disease" and "Coronary Artery Disease in the Young Adult Male." Dr. Beck's topic on Dec. 18 is "Interstitial Pneumonia with Eosinophilia."

Dr. Frederick W. Fitz, F.A.C.P., Chicago, discussed "Sales Psychology for Health and Safety in Industry" at the 42nd National Safety Congress and Exposition, held Oct. 18–22 in Chicago. Dr. Edgar E. Evans, F.A.C.P., Penns Grove, N. J., presented a color, sound motion picture, introducing a new development for protection of personnel in toxic areas, entitled "Use of the Chem-Proof Air Suit," and Dr. Alfred P. Solomon, F.A.C.P., Chicago, took part in a panel discussion, "Why Employees Resist Safety."

Dr. Arthur S. Abramson, F.A.C.P., New York City, presented the 17th Annual Louis Gross Memorial Lecture, sponsored by the Montreal Clinical Society and given in Montreal, Oct. 21. His subject was "Rehabilitation in Geriatric Practice."

Dr. George B. Jerzy Glass (Associate), New York City, addressed the Medical Society of Geneva, Switzerland, Oct. 5, on "The Biochemistry and Physiology of Intrinsic Factor and Its Relation to the Metabolism of Vitamin B_{12}."

Dr. Heinrich Necheles, F.A.C.P., Chicago, discussed "Physiology of the Large and Small Bowel, Clinical Aspects" at the Kansas City Academy of Medicine on Oct. 15.

Dr. Stanley F. Hampton (Associate), St. Louis, was the principal out-of-state speaker at the fall meeting of the Philadelphia Allergy Society, Oct. 27. He discussed "Causes and Treatment of Intrinsic Bronchial Asthma."

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, spoke on a cardiovascular topic at a meeting of the Heart Association of Greater Miami on Oct. 28.

"The Chemotherapy of Pulmonary Infections" was discussed by Dr. William P. Boger, F.A.C.P., Philadelphia; and Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, presented "What Price Antimicrobial Therapy" at the annual meeting of the Medical Society of Delaware, held in Dover, Oct. 11–13.

Dr. Lauren H. Smith, F.A.C.P., Philadelphia, delivered the Academic Lecture at the Sixth Mental Hospital Institute on "Critique of Somatic Therapies" at Minneapolis, Minn., on Oct. 20.

Dr. Benjamin M. Kagan, F.A.C.P., Chicago, Associate Professor of Pediatrics at the University of Illinois College of Medicine, was among the guests of the Georgia Pediatric Society when the association convened in Atlanta, Oct. 28.

Four members of the College were guest speakers at the Maricopa County Conferences on Recent Advances in Medicine, sponsored by the Maricopa County Medical Society in Phoenix, Ariz., Nov. 3–4. Dr. George C. Griffith, F.A.C.P., Pasadena, Calif., presented "Recent Advances in Heart Disease," and Dr. Paul Starr, F.A.C.P., Pasadena, spoke on "Recent Advances in Endocrine and Metabolic Disease." Dr. Gordon Meiklejohn (Associate), Denver, Colo., discussed "Recent Advances in Virus Disease," and Dr. Marcus A. Krupp (Associate), Palo Alto, Calif., delivered a paper entitled "Recent Advances in Liver and Kidney Function Tests."

Dr. Jacques Genest, F.A.C.P., Montreal, was one of the co-authors of a paper on the "Clinical Uses of Rauwolfia," which was presented at a meeting of the Royal College of Physicians and Surgeons of Canada on Oct. 23.

Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, Va., and Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, were guests of the Florida Clinical Diabetes Association at its Second Annual Meeting at Orlando, Oct. 21–22. Dr. Mulholland's subjects were "Diabetes—Its General Management," "Radioactive Isotopes in the Diagnosis and Treatment of Thyroid Disease," "Some of the Complications of Diabetes," "Preoperative and Postoperative Care of the Diabetic Patient," "Indications for Various Insulins and Their Use," and "Cardiovascular Complications." The subjects discussed by Dr. Beardwood included "Diabetic Ketosis," "New Views on Pathology of Diabetes," "Use of Corticotropic Hormones in Diabetes," Hemochromatosis, Newer Concepts in Etiology and Treatment," and "The Juvenile Diabetic Patient." Dr. Beardwood also delivered an address to physicians and laymen on "The Employment of Persons with Diabetes Mellitus," and, together with Dr. Mulholland and various Florida speakers, participated in a panel discussion.

Dr. William B. Tucker, F.A.C.P., Durham, N. C., spoke on "The Shifting Emphasis in Tuberculosis Control" during the 41st Annual Meeting of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Trudeau Society, held in Kansas City, Kans., Oct. 7–9. Drs. James J. Waring, M.A.C.P., Denver, and Julius L. Wilson, F.A.C.P., Philadelphia, were among the participants in a Session on Home Treatment of Tuberculosis. Dr. Oscar A. Sander, F.A.C.P., Milwaukee, was moderator for a Panel on Pulmonary Emphysema.

Dr. Arthur S. Abramson, F.A.C.P., New York City, was Chairman of a Symposium, M.D.A.A. Chapters and the Patient Service Program, which was part of the Third Medical Conference of the Muscular Dystrophy Associations of America that convened Oct. 8–9 in New York City.

"Latest Trends in Hormone Therapy" was discussed by Dr. Grosvenor W. Bissell (Associate), Buffalo, N. Y., at the annual conference of the American Association of Medical Record Librarians in Detroit, Oct. 4–8. Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, also participated in the conference.

Dr. Louis F. Bishop, F.A.C.P., New York City, spoke on "Psychosomatic Aspects of Cardiovascular Surgery (Medical Aspects)" at the First Annual Meeting of the Academy of Psychosomatic Medicine, which was held in New York City, Oct. 8–9.

Dr. Paul S. Rhoads, F.A.C.P., Chicago, was among the out-of-state speakers at the 110th Scientific Assembly of the Northwestern Ohio Medical Association, in Tiffin, Oct. 6. His presentation was entitled "Planning of Antibacterial Management with a Consideration of Pitfalls."

At the annual meeting of the State Medical Society of Wisconsin, Dr. William B. Bean, F.A.C.P., Iowa City, delivered the Lucy Ann Droessel Memorial Lecture of the Wisconsin Heart Association, "Pain in the Chest." Dr. Frederick W. Fitz, F.A.C.P., Chicago, discussed "The Doctor and His Heart." The meeting was held in Milwaukee, Oct. 4–6.

Dr. Clifford J. Barborka, F.A.C.P., Chicago, delivered three of the Sommer Memorial Lectures at the 80th Annual Session of the Oregon State Medical Society, held in Portland, Oct. 13–16. His subjects were "Modern Concepts in Peptic Ulcer Problems," "Management of Poorly Functioning Gallbladder," and "Present Status of Nutritional Deficiency States." Dr. Edward G. Billings, F.A.C.P., Denver, delivered the three Oregon Academy of General Practice Lectures, "Capriciousness of Epilepsy," "Cause of Personality Disorders in the Menopause," and "Anxiety and Thyrotoxicosis." Together with Dr. Barborka, he also participated in a panel discussion.

Dr. Albert A. Brust, Jr. (Associate), Emory University (Ga.) School of Medicine, discussed "Medical Complications" in a Symposium on Complications of Pregnancy, sponsored by the Academy of Medicine of Cincinnati, Oct. 5.

Five members of the College were among the out-of-state speakers who participated in the annual scientific assembly and congress of the New York Academy of General Practice, which was held in Syracuse, Oct. 11–13. Drs. Elliott P. Joslin, M.A.C.P., Howard F. Root, F.A.C.P., and Priscilla White, F.A.C.P., Boston, were the participants in a Symposium on Diabetes (Aspects in Children, Pregnancy, and Surgery). Dr. Raphael Isaacs, F.A.C.P., Chicago, presented "Recent Advances in Anemias," and Dr. Eugene C. Eppinger, F.A.C.P., Boston, spoke on "Problems of Heart Diseases for the General Practitioner."

"Diagnosis and Therapy of Chronic Pulmonary Disease" was the subject considered by Dr. Howard M. Payne (Associate), Professor of Medicine, Howard University College of Medicine, Washington, D. C., when he addressed a meeting of the St. Louis County Medical Society in Virginia, Minn., Oct. 14.

Drs. Harold G. Wolff, F.A.C.P., and Howard A. Rusk, F.A.C.P., New York City, are among those who have delivered lectures in a Series on Psychosomatic Medicine for the General Medical Profession, which is being held under the auspices of the Philadelphia Institute for Education and Research in Psychiatry at the Philadelphia Psychiatric Hospital. On Oct. 28, Dr. Wolff discussed "Life Situations, Emotions, and Disease," and on Dec. 9, Dr. Rusk considered "Emotional Factors in Physical Disability."

Dr. Lloyd F. Craver, F.A.C.P., New York City, spoke on "Some Aspects of Malignant Lymphomas" at the Seventh Annual Cancer Conference for Physicians, sponsored by the Rhode Island Medical Society, Oct. 13, in Providence.

Drs. George E. Burch, Jr., F.A.C.P., New Orleans, and Irvine H. Page, F.A.C.P., Cleveland, participated in "Progress Reports in Cardiovascular Diseases," which was held in Knoxville, Oct. 8–9, under the auspices of the East Tennessee Heart Association. Dr. Burch spoke on "Newer Concepts in Pathogenesis, Diagnosis, and Treatment of Congestive Heart Failure" and "Psychogenic Affections of the Heart," and Dr. Page discussed "Arteriosclerosis."

Drs. John R. Haserick, F.A.C.P., Cleveland, and William W. Frye, F.A.C.P., New Orleans, were among the guest speakers at the 105th Annual Convention of the Indiana State Medical Association, which met in Indianapolis, Oct. 24–27. Their respective topics were "Modern Concepts of Lupus Erythematosus" and "Evaluation of the Antibiotics."

Discussing "Radioactive Isotopes in Diagnosis and Treatment of Heart Disease," Dr. Benedict J. Duffy, Jr. (Associate), Washington, D. C., participated in the Heart Day program at Utica, N. Y., Oct. 28. The program was sponsored by the Utica Academy of Medicine and the Medical Societies of the Counties of Oneida, Herkimer, and Madison.

Dr. E. Cowles Andrus, F.A.C.P., Baltimore, President of the American Heart Association, who discussed "Clinical and Physiological Consequences Following Surgical Treatment of Mitral Stenosis," and Dr. Harold D. Levine, F.A.C.P., Boston, who presented "Modifying Factors in the Diagnosis of Angina Pectoris," were the principal speakers at the Rochester (N. Y.) Academy of Medicine, Oct. 28. The postgraduate teaching day program was jointly sponsored by the Academy, the Heart Committee of the Health Association of Rochester and Monroe County in coöperation with the New York State Department of Health and the Medical Society of the County of Monroe.

In addition to speakers reported in an earlier issue of this journal, Dr. Robert H. Flinn, F.A.C.P., Battle Creek, Mich., also participated in the 22nd Annual Assembly of the Omaha Mid-West Clinical Society, held Oct. 25–28 in Omaha. Dr. Flinn discussed "Federal Civil Defense Medical Programs."

Dr. Roy W. Scott, F.A.C.P., Cleveland, was the speaker at a banquet sponsored by the Kansas University Medical Alumni Association and held Oct. 6 in Kansas City during the Fall Conference of the Kansas City Clinical Society. His topic was "Prognosis in Coronary Artery Disease."

Dr. George A. Hellmuth, F.A.C.P., Milwaukee, spoke on "Emergency Treatment of Cardiac Arrhythmia" during the annual Scientific Assembly of the Illinois Academy of General Practice, held in Chicago, Oct. 26–28.

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, was guest lecturer of Asociacion Medica de Puerto Rico, Santurce, P. R., Oct. 4–8. In addition, Dr. Leaman addressed the third- and fourth-year classes at the University of Puerto Rico, San Juan, and made rounds at the Veterans Administration Hospital on the Island.

Drs. Ray F. Farquharson, F.A.C.P., Toronto, College Governor for Ontario, and John P. Gemmell (Associate), Winnipeg, participated in the 63rd Annual Meeting of the Association of Life Insurance Medical Directors of America, held in Toronto, Oct. 12–14. Their respective subjects were "The Present Medical Situation" and "Radioactive Isotopes and Insurability."

Speaking on "Problems in Diagnosis of Thyroid Disease. Medical Emergencies," Dr. John E. Peterson, F.A.C.P., Los Angeles, was among the out-of-state speakers at the Fifth Annual Scientific Assembly of the Florida Academy of General Practice in Orlando, Oct. 17–18. Dr. George T. Harrell, Jr., F.A.C.P., Dean and Professor of Medicine at the University of Florida School of Medicine, was also a guest of the society.

Drs. Theodore L. Badger, F.A.C.P., and C. Sidney Burwell, F.A.C.P., both of Boston, addressed the 67th Meeting of the American Clinical and Climatological Association, which met under the Presidency of Dr. Robert L. Levy, F.A.C.P., New York City, at Lake Placid, N. Y., Oct. 14–16.

Under the Presidency of Dr. Hugh R. Leavell, F.A.C.P., Boston, the American Public Health Association held its 82nd Annual Meeting in Buffalo, N. Y., Oct. 11–15. Dr. John R. Paul, F.A.C.P., New Haven, Conn., participated in the Conference of Professors of Preventive Medicine, and Dr. Orren D. Chapman, F.A.C.P., Syracuse, N. Y., was the dinner speaker for the Conference of State and Provincial Public Health Laboratory Directors.

Two Associates of the College from New York City, Drs. Joseph G. Benton and Menard M. Gertler, were among the guest speakers at the Second Annual Seminar in Postgraduate Medicine sponsored by the Philadelphia Academy of General Practice and held Oct. 18. Their respective subjects were "Rehabilitation of the Cardiac" and "Coronary Artery Disease in Young Adults."

Drs. William D. Robinson, F.A.C.P., Ann Arbor, Mich., L. Maxwell Lockie, Sr., F.A.C.P., and Bernard M. Norcross, Jr., F.A.C.P., Buffalo, N. Y., took part in a discussion of "Rheumatic Diseases" at the annual fall meeting of the Sixth Councilor District, held in Akron, Ohio, Oct. 27.

Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., President of the American Medical Association, delivered an address at the 24th Annual Fall Conference of the Oklahoma City Clinical Society, Oct. 25–28. Among the guests participating in the teaching program were Drs. William S. Middleton, M.A.C.P., Madison, Wis., and William G. Sauer, F.A.C.P., Rochester, Minn.

On Nov. 10, Dr. Martin was the banquet speaker at a dinner following the dedication of the new Bluefield (W. Va.) Sanitarium Clinic.

At the annual meeting of the American Dietetic Association, held in Philadelphia, Oct. 26–29, Dr. Paul György, F.A.C.P., Philadelphia, discussed "Trends and Advances in Infant Nutrition." Dr. Robert M. Kark, F.A.C.P., Chicago, participated in a discussion of "Non-nutritive Sweeteners." Among the other physicians participating in the program were Drs. George H. Gehrmann, F.A.C.P., Wilmington, Del., and William H. Sebrell, Jr., F.A.C.P., Bethesda, Md.

Dr. Harold G. Wolff, F.A.C.P., New York City, whose subject was "Headache Mechanisms," delivered the Eighth Annual Lectureship sponsored by the Sigma Chapter of Phi Delta Epsilon fraternity at Temple University School of Medicine, Philadelphia, Oct. 27.

Dr. Walter C. Alvarez, F.A.C.P., Chicago, delivered the Stanley R. Truman Lecture, "Unrecognized Psychotic Conditions," at the Scientific Assembly of the California Academy of General Practice, which met in Los Angeles, Oct. 24–27. Dr. W. Paul Holbrook, F.A.C.P., Tucson, Ariz., who spoke on "Medical Management of Arthritis," was among the other out-of-state speakers.

Changes in Fees and Dues for A.C.P. Members Beginning January 1, 1955

The American College of Physicians up to this time has maintained the same fees and dues that were in effect as much as 30 years ago. It probably has been the only medical organization that has established such a record, although its services to its members and to the medical profession far exceed those of most other societies. The *Annals of Internal Medicine,* for which the non-member subscription price is $10.00 in the United States and Canada, is given without further charge to all members who

pay dues. Its postgraduate courses are provided to members for one-half the price charged to non-members. There is no registration fee to members for attendance at its Annual Sessions, which constitute the most important and extensive postgraduate week in Internal Medicine in North America. Other services and advantages provided members are numerous and extensive.

After the most careful study and in consideration of many additional activities being added, the Board of Regents on November 14, 1954, decided to increase the dues moderately. The initiation fee for Fellowship will not be affected. Associate dues for practicing clinicians will be advanced from $15.00 to $18.00; Fellowship dues for practicing clinicians increased from $20.00 to $25.00; dues of both Associates and Fellows who are full-time teachers or research workers in institutions not subject to profit, members of the Medical Corps of the Air Force, Army, Navy, Public Health Service and Veterans Administration remain unchanged, $12.00 annually.

At the discretion of the Board of Regents, without publicity, initiation fees or annual dues may be remitted in whole or in part, as in the case of men engaged in purely scientific research, full-time medical teaching, the public service, or in the event of any Master, Fellow or Associate suffering serious disability or financial reverses. In case of change of status to provide practice or similarly remunerative occupation, the Board of Regents may require the payment of the usual annual dues.

Life Membership. Until 1933, the life membership fee amounted to $500.00. At that time a new life membership plan with varying fees according to age was adopted. Beginning January 1, 1955, the following life membership fees become effective: (The following fees are additional to the original initiation fee)

Up to and including age 50	$375.00
Ages 50 to 60 inclusive	Number of years between current age and 65, times the annual dues
Age 50—15 yrs. × $25	$375.00
51—14 yrs. × $25	350.00
52—13 yrs. × $25	325.00
53—12 yrs. × $25	300.00
54—11 yrs. × $25	275.00
55—10 yrs. × $25	250.00
56— 9 yrs. × $25	225.00
57— 8 yrs. × $25	200.00
58— 7 yrs. × $25	175.00
59— 6 yrs. × $25	150.00
Age 60, and thereafter	125.00 minimum

The Life Membership Fee entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual and Regional Sessions, to the *Annals of Internal Medicine*, the Directory and other publications. *Life Members are active members for life.* This plan affords the member an opportunity of paying his full dues during his productive years and while his income is greatest, thus avoiding the burden of dues later in life. The life membership fee is deductible on federal income tax.

ELECTION TO MEMBERSHIP IN THE AMERICAN COLLEGE OF PHYSICIANS

At a meeting of the Board of Regents, held in Philadelphia, Nov. 14, 1954, the following candidates were elected to membership in the College (Fellows indicated in FULL CAPITALS; Associates, Lower Case):

HORACIO ABASCAL ..... Havana, Cuba
Robert Featherston Ackerman ..... Memphis, Tenn.
Leonard Carl Akman ..... Baltimore, Md.

THOMAS PATTISON ALMY ..... New York, N. Y.
Thomas Page Anderson ..... Hanover, N. H.
Gould Arthur Andrews, Jr. ..... Oak Ridge, Tenn.
William Antine ..... Brooklyn, N. Y.
ALLIE KEARNEY ATKINSON ..... Great Falls, Mont.
Perry Richard Ayres ..... Columbus, Ohio

Theodore Bacharach ..... M.C., U. S. Army
William Ryland Bailey, Jr. ..... Pittsburgh, Pa.
John Langum Bakke ..... Seattle, Wash. (V.A.)
Warren Philip Ball ..... Muncie, Ind.
Volney Bryce Ballard ..... Kansas City, Mo.
John Henry Barksdale, Jr. ..... Statesboro, Ga.
Richard Henry Barr ..... San Francisco, Calif.
J(OSEPH) GORDON BARROW ..... Atlanta, Ga.
LEO HENRY BARTEMEIER ..... Baltimore, Md.
William Stanhope Baum ..... Bethesda, Md. (U.S.P.H.S.)
Harold Bedell ..... New York, N. Y.
Gilbert Arthur Beirne ..... San Francisco, Calif.
JOHN LATHAM BELL ..... Honolulu, T. H.
EUGENE HUNTINGTON BENSON, JR. .... El Centro, Calif.
Erwin Edward Benzier ..... Rego Park, N. Y.
Arthur Walter Berg ..... Portland, Ore.
Robert Berghan ..... Spokane, Wash.
BERNARD HARVEY BERMAN ..... Washington, Pa.
RICHARD JOHN BING ..... Birmingham, Ala.
GROSVENOR WILLSE BISSELL ..... Buffalo, N. Y. (V.A.)
Charles Richards Blackburn ..... Boise, Idaho
Herman Leonard Block ..... Fitchburg, Mass.
William Joseph Block, Jr. ..... San Antonio, Tex.
William Allan Blodgett ..... Louisville, Ky.
Arnold George Blumberg ..... Manhasset, N. Y.
William Holmes Bond ..... Indianapolis, Ind.
Frank Cutchin Bone ..... Orlando, Fla.
Donald Thompson Book ..... M.C., U. S. Army
KATHARINE R. BOUCOT ..... Philadelphia, Pa.
Saul Philip Bralow ..... Philadelphia, Pa.
Dorothy Brewer ..... San Antonio, Tex.
Albin Monroe Brixey, Jr. ..... Joliet, Ill.
Henry Brown ..... New Rochelle, N. Y.
Elwood Buchman ..... Iowa City, Iowa (V.A.)
Robert Ervin Buck ..... San Luis Obispo, Calif.
Howard Albert Buechner ..... New Orleans, La. (V.A.)

Massimo Calabresi ..... West Haven, Conn. (V.A.)
Robert Allen Campbell ..... Walla Walla, Wash.
Nicholas Louis Campione ..... Chicago, Ill.
Elmer Otto Carlson ..... Ontario, Calif.
Ewen Pollock Carruthers ..... Kelowna, B. C., Can.
Carlton Jerome Casey ..... Kecoughtan, Va. (V.A.)
Rowe Anthony Castagno ..... Hartford, Conn.
A. Zerne Chapman ..... Mussoorie, India
Norman Chassin ..... Kenmore, N. Y.
Melvin M. Chertack ..... Chicago, Ill.

JACK SHELDON CHUDNOFF ..... Los Angeles, Calif.
Duncan William Clark ..... Brooklyn, N. Y.
HARLEY ERNEST CLUXTON, JR. ..... Chicago, Ill.
GEORGE CHARLES COE ..... Chicago, Ill.
WILLIAM LEO COFFEY, JR. ..... Milwaukee, Wis.
NATHANIEL ABRAHAM COHEN ..... Forest Hills, N. Y.
LAWRENCE REDMAN COKE ..... Winnipeg, Man., Can.
Richard Lemuel Cole ..... Fort Harrison, Mont. (V.A.)
EUGENE LEON COODLEY ..... Los Angeles, Calif.
William Marion Cooper ..... Pittsburgh, Pa.
Dale Homer Correa ..... Minneapolis, Minn.
DAVID BAIRD COURSIN ..... Lancaster, Pa.
Mitchel Dale Covel ..... Beverly Hills, Calif.
Walter Bedford Cox ..... Missoula, Mont.
Louis Aleck Craig, Jr. ..... Washington, D. C.
Robert Henry Craig ..... Waterloo, Ont., Can.
Ernest Samuel Cross, Jr. ..... Baltimore, Md.
MILTON CUTLER ..... Hammonton, N. J.

William Monroe Daily ..... McKinney, Tex. (V.A.)
John Maher Daley ..... New York, N. Y.
Fernand Joseph Dastugue, Jr. ..... Biloxi, Miss. (V.A.)
Winthrop Newbury Davey ..... Ann Arbor, Mich.
Joseph Davis ..... Castle Point, N. Y. (V.A.)
Albert I. C. DeFriez ..... Boston, Mass.
William Paul Deiss, Jr. ..... Durham, N. C. (V.A.)
Owen Deneen ..... Bloomington, Ill.
RALPH MYERS DENHAM ..... Louisville, Ky.
Stephen Henri Deschamps ..... Bridgeport, Conn.
Murray Allen Diamond ..... Washington, D. C. (U.S.P.H.S.)
Frank Theodore Dienst, Jr. ..... Shreveport, La.
Thomas Claude Donald, Jr. ..... Anniston, Ala.
John Munroe Douglas ..... Charlotte, N. C.
DANIEL FRANCIS DOWNING ..... Philadelphia, Pa.
Oscar Herman Dreskin ..... Cincinnati, Ohio
Frederick Cecil Duffy ..... Pittsburgh, Pa.
Alfred Leslie Duncombe ..... Brockton, Mass.

Archie Yelverton Eagles ..... Ahoskie, N. C.
ROBERT EDWARD ECKARDT ..... Linden, N. J.
Walton Merideth Edwards ..... M.C., U. S. Army
Max Eil ..... Forest Hills, N. Y.
Edward Ira Elisberg ..... Chicago, Ill.
Robert Wood Emerick ..... Muskegon, Mich.
Milton Ende ..... Petersburg, Va.
Rudolf C. H. Engel ..... Oregon City, Ore.
Joseph Robbins Evans ..... Salt Lake City, Utah

ROBERT MAGWOOD FAWCETT ..... Devils Lake, N. D.
John Gifford Fee ..... St. Paul, Minn.
Joseph Sidney Feibush ..... New York, N. Y.
Bruce Collier Ferguson ..... Boston, Mass. (V.A.)
Charles Fisch ..... Indianapolis, Ind.
William John Henry Fischer, Jr. ..... Providence, R. I.
EDISON DAVID FISHER ..... Los Angeles, Calif.

SEYMOUR FISHER ..... Phoenix, Ariz. (V.A.)
Alfred Paul Fishman ..... New York, N. Y.
Edna M. J. Fitch ..... Madison, Wis.
Reginald Heber Fitz ..... Denver, Colo.
Thomas James Fitzpatrick ..... Joliet, Ill.
David Jonas Flicker ..... Newark, N. J.
James Hennigar Follette ..... Santa Monica, Calif.
Richard Foulk ..... M.C., U. S. Navy
NOBLE OWEN FOWLER, JR. ..... Atlanta, Ga.
James Bruce Frain ..... Winnipeg, Man., Can.
BYRON FRANKLIN FRANCIS ..... Seattle, Wash.
William Donald Franklin ..... Bayside, N. Y.
IRVING FREEMAN ..... Baltimore, Md. (V.A.)
Henry David Freiman ..... Philadelphia, Pa.
Arthur Bancroft French ..... Salt Lake City, Utah

Lawrence Herman Gahagan ..... New York, N. Y.
John Veiller Galgiani ..... San Francisco, Calif.
Solomon Garb ..... New York, N. Y.
Carl Clinton Gardner, Jr. ..... Columbia, Tenn.
Maurice Carl Gephardt ..... Muskogee, Okla.
ALEXANDER GERBER ..... Brooklyn, N. Y.
Ray Wallace Gifford, Jr. ..... Silver Springs, Md.
JOHN STUART GILSON ..... Great Falls, Mont.
Morton Aaron Goldmann ..... Chicago, Ill.
David Henry Goldstein ..... New York, N. Y.
Joe Golenternek ..... Beverly Hills, Calif.
Herbert Lloyd Goodman ..... Detroit, Mich.
GILBERT SAUL GORDAN, JR. ..... San Francisco, Calif.
Douglas Littleton Gordon ..... New Orleans, La.
Martin Eli Gordon ..... West Haven, Conn. (V.A.)
Robert Stanton Gordon ..... New Haven, Conn.
Ralph Daniel Gorman ..... San Francisco, Calif.
Walter Samuel Graf ..... Los Angeles, Calif.
William Casper Grater ..... Dallas, Tex.
David Haynie Greegor ..... Columbus, Ohio
ELIZABETH GRIMM ..... Billings, Mont.
CHRISTIAN GRONBECK, JR. ..... M.C., U. S. Army
SILVIO MARIO GUGLIELMELLI ..... Brooklyn, N. Y.
Charles Herman Gutenkauf ..... Des Moines, Iowa

PAUL STICKNEY HAGEN ..... Minneapolis, Minn. (V.A.)
Bernard Lingo Hallman ..... Atlanta, Ga.
Seymour Lionel Halpern ..... New York, N. Y.
William James Hand ..... Chicago, Ill.
Fred Heath Hanold ..... Albuquerque, N. M.
Wilford Reeve Hansen ..... Louisville, Ky.
Mark C. L. Hanson ..... Minneapolis, Minn.
Edward Everett Harnagel ..... Los Angeles, Calif.
William Joseph Harrington ..... St. Louis, Mo.
HAROLD IRA HARVEY ..... Berkeley, Calif.
John Collins Harvey ..... Baltimore, Md.
JOHN ROGER HASERICK ..... Cleveland, Ohio
Daniel William Hayes ..... New Orleans, La.

Thomas Sylvester Healy ..... Portland, Ore. (V.A.)
WILLIAM ISAAC HEINE ..... Philadelphia, Pa.
Aaron Jonah Heisen ..... Imlaystown, N. J.
MILTON R. HEJTMANCIK ..... Galveston, Tex.
EMANUEL HELLMAN ..... New York, N Y.
Robert Albert Helm ..... Cincinnati, Ohio
Basil Lloyd Hession ..... London, Ont., Can.
EDWARD CLYDE HEYDE ..... Vancouver, Wash.
WALTER HENRY PHILIP HILL ..... Montreal, Que., Can.
IRWIN McAMMOND HILLIARD ..... Saskatoon, Sask., Can.
JAMES HARVEY BRUCE HILTON ..... Ottawa, Ont., Can.
Carl Raymond Hines, Jr. ..... Evanston, Ill.
Robert Edgar Hodges ..... Iowa City, Iowa
Walter Frederick Hoeppner ..... Chicago, Ill.
FREDERICK WILLIAM HOFFBAUER ..... Minneapolis, Minn.
Leo Edward Hollister ..... Palo Alto, Calif. (V.A.)
Evans Zack Hornberger, Jr. ..... Fort Smith, Ark.
R(OBERT) PALMER HOWARD ..... Oklahoma City, Okla.
James Theodore Howell ..... Detroit, Mich.
JOHN GERARD HOWLETT ..... Montreal, Que., Can.
JOHN PERRY HUBBARD ..... Philadelphia, Pa.
ROY SEARS HUBBS ..... Palo Alto, Calif. (V.A.)
Harry Laymond Hunter ..... Chicago, Ill.
JOHN WILLIS HURST ..... Emory University, Ga.
Mayer Hyman ..... Tucson, Ariz.

John Lowell Ilsley ..... Claremont, Calif.
Thomas Witherspoon Inmon ..... M.C., U. S. Army
John Martin Irvin ..... Monroe, Wis.
Lloyd Taiji Iseri ..... Detroit, Mich.

George Gee Jackson ..... Chicago, Ill.
Leonard Joseph Janchar ..... Barberton, Ohio
EDWARD JOHN JARUSZEWSKI, SR. ..... M.C., U. S. Navy
Edwin Joseph Jensen ..... Coral Gables, Fla.
Joe Haines Jewett ..... Indianapolis, Ind.
Joy Ruth Joffe ..... Seattle, Wash.
Jarone William Johnson ..... Los Angeles, Calif.
Carl Candler Jones ..... Atlanta, Ga.
Ralph Jones, Jr. ..... Philadelphia, Pa.
Thurman Thomas Justice, Jr. ..... Gulfport, Miss.

ALFRED KAHN, JR. ..... Little Rock, Ark.
BERNARD SAMUEL KAHN ..... New York, N. Y.
Charles Fairweather Kane ..... Brockton, Mass.
Leon B. Katz ..... Pittsburgh, Pa.
GEORGE LEONARD KAUER, JR. ..... New York, N. Y.
Harold Keen ..... Bowling Green, Ky.
Robert Wilson Kelley ..... St. Louis, Mo.
Edward Christopher Kenney ..... M.C., U. S. Navy
Jack Munro Kenyon ..... Toledo, Ohio
PAUL KIMMELSTIEL ..... Charlotte, N. C.
Janet Kinney ..... Chicago, Ill.
WALTER MURRAY KIRKENDALL ..... Iowa City, Iowa (V.A.)
Benjamin Franklin Klaumann ..... Long Beach, Calif. (V.A.)

Arthur Merrill Knight, Jr. ..... Waycross, Ga.
Harvey Coles Knowles, Jr. ..... Cincinnati, Ohio
John Frederick Koester ..... New York, N. Y.
Felix Oscar Kolb ..... San Francisco, Calif.
MAXWELL HOWARD KOLODNY ..... New York, N. Y.
George Eli Koury ..... Burlington, N. C.
SIDNEY OURIN KRASNOFF ..... Philadelphia, Pa.
E(DWARD) CHARLES KUNKLE ..... Durham, N. C.

Roland Paul Ladenson ..... Columbia, Mo.
Gordon Richard Lamb ..... Oakland, Calif.
Vance Ball Lancaster ..... Battle Creek, Mich.
Milton Elliot Landman ..... Bloomfield, N. J.
KURT LANGE ..... New York, N. Y.
Ward Laramore ..... Indianapolis, Ind. (V.A.)
John Charles Larkin, Jr. ..... Memphis, Tenn., (V.A.)
Charles Andrew Laubach, Jr. ..... Danville, Pa.
MAURICE KAMM LAURENCE ..... Swampscott, Mass.
Charles Edward Law ..... Washington, D. C.
HOMER EDSON LAWRENCE ..... Concord, N. H.
GERALD O. LAXSON ..... Sheridan, Wyo. (V.A.)
Edgar Leifer ..... New York, N. Y.
GEORGE BRUCE LEMMON, JR. ..... Springfield, Mo.
Gerson Theodore Lesser ..... New York, N. Y.
Macy Irving Levine ..... Pittsburgh, Pa.
George Levy ..... Chicago, Ill.
Herbert Daniel Lewis ..... New Haven, Conn.
Jonah Genwin Li ..... San Francisco, Calif.
THOMAS NORWOOD LIDE ..... Winston-Salem, N. C.
Marvin Lillian ..... Bridgeport, Conn.
BERNARD M. LIPSCHULTZ ..... Phoenix, Ariz. (V.A.)
LESTER LIPSON ..... Montieello, N. Y.
Virgil Loeb, Jr. ..... St. Louis, Mo.
Marion Cotton Loizeaux ..... Albany, N. Y. (V.A.)
George Walter Loomis ..... Omaha, Nebr.
CLAYTON GARR LOOSLI ..... Chicago, Ill.
Vincent Logan Love ..... Marion, Ind.
William DeLoss Love ..... New Orleans, La.
DOSS OWEN LYNN ..... M.C., U. S. Army
BENJAMIN HARRY LYONS ..... Winnipeg, Man., Can.

George Edmond MacDonald ..... Boston, Mass.
Harold Harrington MacGilpin, Jr. ..... Worcester, Mass.
Hubert Francis MacInnis ..... Camrose, Alta., Can.
THOMAS KEITH MacLEAN ..... Vancouver, B. C., Can.
Dorothy Macy, Jr. ..... Philadelphia, Pa.
Norman Morton Mann ..... Hartford, Conn.
Andrew Menges Margileth ..... M.C., U. S. Navy
Robert Francis Maronde ..... Pasadena, Calif.
Maurice Delbert Marsh ..... Cincinnati, Ohio
Thomas Wilson Martin ..... Pittsburgh, Pa.
Robert James Marvel ..... Indianapolis, Ind.
PAUL EMIL MATTMAN ..... Detroit, Mich.
William Paul McCarthy ..... Trenton, N. J.

James Kenneth McCorkle ..... St. Petersburg, Fla.
Herbert Irving McCoy ..... La Jolla, Calif.
Samuel Kenneth McIlvanie ..... Spokane, Wash.
William Bernard McIntyre ..... Detroit, Mich.
CHARLES RALPH MESSELOFF ..... New York, N. Y.
Roger Gavitt Metcalf ..... Manila, P. I. (V.A.)
Robert Matthew Metcalfe ..... Crossville, Tenn.
Joseph Cahn Meyer ..... Chicago, Ill.
MAX BENJAMIN MILBERG ..... Brooklyn, N. Y.
CONN LEWIS MILBURN, JR. ..... M.C., U. S. Army
Annabel Bonnet Miller ..... Buffalo, N. Y. (V.A.)
JOHN MILNE ..... Hanover, N. H.
ALBERT MILZER ..... Chicago, Ill.
PAUL FLOYD MINER ..... Boise, Idaho
JOHN HARRINGTON MITCHELL ..... Columbus, Ohio
John Wendell Moberly ..... Dubuque, Iowa
Coleman Mopper ..... Detroit, Mich.
Francis Marion Morgan ..... M.C., U. S. Navy
Frank Mattison Morgan, Jr. ..... Glendale, Calif.
JOHN LLOYD MORGAN ..... Emporia, Kans.
Louis C. Morris ..... Chicago, Ill.
John Frederick Mueller ..... Cincinnati, Ohio
Martin Julius Mueller ..... Kansas City, Mo.
ERNEST ERIC MUIRHEAD ..... Dallas, Tex.
Austin Edward Mutz ..... Denver, Colo.
DANIEL WILBUR MYERS ..... Detroit, Mich.

Henry Blum Nachtigall ..... New York, N. Y.
David Harry Naimark ..... M.C., U. S. Army
DeWITT NEIGHBORS ..... Fort Worth, Tex.
ROBERT STUART NELSON ..... M.C., U. S. Army
Rex Harlan Newton ..... Pittsburgh, Pa.
Byron Atlee Nichol ..... M.C., U. S. Army
Thomas Arthur Noble ..... Blue Island, Ill.
William Joseph Noble ..... Brooklyn, N. Y.

Sidney Olansky ..... Atlanta, Ga. (U.S.P.H.S.)
Matthew Anthony Olivo ..... Camden, N. J.
James Newton Owens, Jr. ..... Oklahoma City, Okla.

Gordon Stanley Paulson ..... Rapid City, S. D.
ARPAD PAUNCZ ..... Downey, Ill. (V.A.)
Sabin Crawford Percefull ..... Denver, Colo.
Paul Thomas Perugini ..... New Rochelle, N. Y.
Henry Augustus Peters ..... Madison, Wis.
Elroy Russell Peterson ..... Ames, Iowa
Wesley Leroy Peterson, Jr. ..... Sarasota, Fla.
DONALD MARION PILLSBURY ..... Phila'elphia, Pa.
Philip Lansdale Pillsbury ..... San Francisco, Calif.
Clifford George Pilz ..... Chicago, Ill. (V.A.)
Kermit Leonard Pines ..... New York, N. Y.
Irvin Chaffee Plough ..... M.C., U. S. Army
Donald Edward Pohl ..... Austin, Tex.
Mark Moses Pomaranc ..... Chicago, Ill.

Pierre Patillo Poole ..... Brownsville, Tex.
ROLF FALK POSER ..... Columbus, Wis.
Edward Rudolph Posner, Jr. ..... Des Moines, Iowa
Samuel Franz Potsubay ..... Holyoke, Mass.
SAMUEL HERSCHEL PROGER ..... Boston, Mass.

ADOLPH POST RAAB ..... Brooklyn, N. Y.
Raymond Victor Randall ..... Rochester, Minn.
Charles Edward Rankin ..... Lexington, Ky.
Rudolph Edward Reichert, Jr. ..... Ann Arbor, Mich. (V.A.)
CHARLES HAMILTON REID, JR. ..... Winston-Salem, N. C.
Jack Reiss ..... Coral Gables, Fla. (V.A.)
LAWRENCE BERKLEY REPPERT ..... San Antonio, Tex.
Renato Augustus Ricca ..... Glastonbury, Conn.
John Sidney Rice ..... M.C., U. S. Army
Walter Donald Roberts ..... Austin, Tex.
Elrie Parker Rodgers ..... Columbia, Mo.
JACK DAVIDSON ROSENBAUM ..... Boston, Mass. (V.A.)
ALVIN A. ROSENBERG ..... Morristown, N. J.
Alfred Harris Rosenblum ..... Chicago, Ill.
SIDNEY BENJAMIN ROSENBLUTH ..... New York, N. Y.
Robert Charles Rosenquist ..... Loma Linda, Calif.
Ernest Tuttle Rouse ..... St. Louis, Mo.
JOHN HENRY ROWLAND ..... New Brunswick, N. J.
Edward Rubenstein ..... San Mateo, Calif.
JACK ARTHUR RUDOLPH ..... Miami, Fla. (V.A.)
Joseph John Rupp ..... Philadelphia, Pa.
Charles Mark Ryan ..... Sioux City, Iowa

Richard Alfonso Saavedra ..... Chicago, Ill. (U.S.P.H.S.)
JULIUS JOHNSON SACHS ..... Hartford, Conn.
Milton Herman Saier ..... Palo Alto, Calif.
Herbert Andrew St. John ..... West Englewood, N. J.
Irwin Salkin ..... North Hollywood, Calif.
James Allen Salmons ..... San Francisco, Calif. (U.S.P.H.S.)
Harold Sidney Sandhaus ..... Jamaica, N. Y.
Gordon Armstrong Saunders ..... Arlington, Mass.
JAMES GEORGE SAWYER ..... Butte, Mont.
Robert Lawrence Schaefer, Jr. ..... Detroit, Mich.
W(OODROW) WILSON SCHIER ..... Brooklyn, N. Y. (V.A.)
Arthur Schifrin ..... New York, N. Y.
Henry Kramer Schoch ..... Ann Arbor, Mich. (V.A.)
Donald August Scholz ..... Rochester, Minn.
Saul Alvin Schwartz ..... New York, N. Y.
THEODORE BENONI SCHWARTZ ..... Durham, N. C. (V.A.)
Ralph Carmen Scott ..... Cincinnati, Ohio
Joseph Selman ..... Tyler, Tex.
Holbrooke Stroud Seltzer ..... Ann Arbor, Mich.
Richard Carr Sexton, Jr. ..... Knoxville, Tenn.
Robert William Sharp ..... M.C., U. S. Navy
Murray Bernard Sheldon, Jr. ..... Cincinnati, Ohio
WALTER BROWN SHELLEY ..... Philadelphia, Pa.
Jacques Lawrence Sherman ..... M.C., U. S. Army
Solomon Sherry ..... St. Louis, Mo.

John Adrian Shively ..... Bluffton, Ind.
Bernard Silber ..... Redwood City, Calif.
WARREN KOUSCH SIMMONS ..... Rhinelander, Wis.
Robert Bentham Simons ..... Lexington, Ky.
Jerome Simson ..... New York, N. Y.
John Heffron Sisson ..... Boston, Mass.
Oren Tenner Skouge ..... Fort Harrison, Mont. (V.A.)
Alice Lorraine Smith ..... Dallas, Tex.
Luther Edward Smith ..... Donelson, Tenn.
ISIDORE SNAPPER ..... Brooklyn, N. Y.
Gordon Lloyd Snider ..... Chicago, Ill.
Francis Augustine Spellman ..... Togus, Maine (V.A.)
George Geneser Spellman ..... Sioux City, Iowa
John Keith Spitznagel ..... M.C., U. S. Army
Joseph Antonio Splendido ..... Philadelphia, Pa.
Stanford D. Splitter ..... Berkeley, Calif.
MAXWELL SPRING ..... New York, N. Y.
John Foster Stegeman ..... Athens, Ga.
Roger William Steinhardt ..... New York, N. Y.
Robert Arleth Stier ..... Spokane, Wash.
Chester Sidney Svigals ..... New York, N. Y.

Peter Jacob Talso ..... Chicago, Ill.
Barrett Learned Taussig ..... St. Louis, Mo.
Richard Ray Taylor ..... M.C., U. S. Army
William Ryan Tench ..... Clearwater, Fla.
Paul Erhard Teschan ..... M.C., U. S. Army
John Marshall Thayer ..... Millbrae, Calif.
Charles Archer Thompson ..... Texarkana, Ark.
WILLIAM PAUL THOMPSON ..... Los Angeles, Calif.
Alphonse Emanuel Timpanelli ..... New York, N. Y.
John Covington Tinsley, Jr. ..... Columbia, Mo.
Fred Francis Tirella ..... Bristol, Conn.
Jerome Sanford Tobis ..... New York, N. Y.
Albert Tomasulo ..... Dayton, Ohio (V.A.)
Frank Edwin Trobaugh, Jr. ..... St. Louis, Mo.

PAUL ANTON VAN PERNIS ..... Rockford, Ill.
Hiram Vazquez-Milan ..... San Juan, P. R.
Joseph Robert Vivas ..... M.C., U. S. Army

Philip Franklin Wagley ..... Baltimore, Md.
ARNOLD LOUIS WAGNER ..... Evanston, Ill.
DANIEL JOHN WALIGORA ..... M.C., U. S. Army
Herman Hervey Walker ..... Linesville, Pa.
Robert Bryant Walker ..... Toledo, Ohio
Robert LeRoy Wall ..... Columbus, Ohio
Ralph Oliver Wallerstein ..... San Francisco, Calif.
Robert Solomon Wallerstein ..... Topeka, Kans.
Louis Emmerson Ward ..... Rochester, Minn.
MALCOLM STUART McNEAL WATTS .... San Francisco, Calif.
George Jerome Wayne ..... Los Angeles, Calif.
Gustave Fred Weber ..... New Orleans, La.
Bertram Allen Weeks ..... M.C., U. S. Army

William Edmonds Weems ..... Laurel, Miss.
George Elliot Welch ..... New Orleans, La.
John Lewis Welch ..... Medford, Ore.
Charles Weller ..... Larchmont, N. Y.
Keith Edgar Weller ..... Grand Rapids, Mich.
Joseph Erskine Welsh, Jr. ..... Menlo Park, Calif.
Elizabeth McNaughton Main Welty ..... Spokane, Wash.
D(ENIS) NALDRETT WHITE ..... Kingston, Ont., Can.
James Kenneth Wiggins ..... Fort Worth, Tex.
Howard Max Wikoff ..... Crookston, Minn.
Richard Sloan Wilbur ..... Palo Alto, Calif.
Daniel Metzger Wilkins ..... Pittsburgh, Pa.
Robert Norman Williams ..... Ontario, Calif.
JAMES GARNETT WILLIS ..... Fredericksburg, Va.
Edward Orton Willoughby ..... Hines, Ill. (V.A.)
C(larence) Paul Winchell ..... Minneapolis, Minn.
JOSEPH ALCANTARA WINN ..... Brooklyn, N. Y. (V.A.)
JOHN R. WINSTON ..... Temple, Tex.
Richard Erwin Winter ..... New York, N. Y.
Keith Burton Witte ..... Monroe, Wis.
LESTER EUGENE WOLD ..... Fargo, N. D.
JULIUS WOLF ..... New York, N. Y. (V.A.)
Kenneth Rau Woolling ..... Indianapolis, Ind.

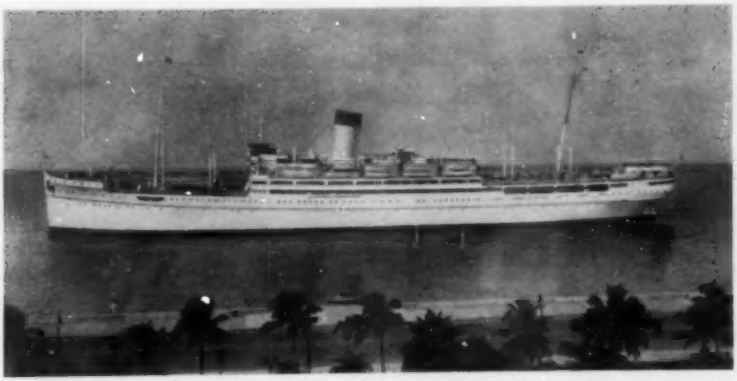
STEPHEN BENNETT YOHALEM ..... New York, N. Y.

Abraham Zelony ..... Patchogue, N. Y.
Leslie Zieve ..... Minneapolis, Minn. (V.A.)
Frederick Ellis Zimmer ..... Danville, Pa.
HORACE HELMUT ZINNEMAN ..... Minneapolis, Minn. (V.A.)

A.C.P. Post-Convention Cruise to Nassau and Havana
April 29–May 9, 1955

Following the Thirty-Sixth Annual Session of the American College of Physicians at Philadelphia, April 25–29, 1955, there will be a post-convention cruise to Nassau and Havana, using the *SS Nassau* of the Incres-Nassau Line. This 573 foot, 24,400 ton ship is fully air conditioned, has two outdoor swimming pools, exceptionally ample desk space, and the usual deck sports, such as trap shooting, shuffleboard, horse racing, etc. All rooms set aside for the College group have shower or bath and toilet, with the exception of three or four minimum rate rooms which have toilet only. The ship will be the home of the party for the entire trip. A scientific program will be arranged both aboard ship and at Havana, the cruise being an integral part of the 1955 Annual Session, thus entitling physicians to deduction of expenses on income returns. Special arrangements have been made to allow ample time for transfer from Philadelphia to New York on Friday evening after adjournment of the Program. The itinerary will be:

Friday, April 29	Embarkation, Pier 42, Foot of Morton St., N. Y. C.	9–10 p.m.
	SS Nassau will sail	10:30 p.m.
Saturday, April 30	Cruising enroute Nassau	
Sunday, May 1	Cruising enroute Nassau	



SS Nassau.

Lounge, *SS Nassau.*

Double outside stateroom, *SS Nassau.*

Dining Salon, *SS Nassau*

Nassau, Bahamas—Public Square and Government Buildings

Gregory's Arch is typical of Nassau's quaint charm and easy way of life.

Luncheon will be served one day at the British Colonial Hotel whose Beaches are depicted above.

Morro Castle, at Entrance to Havana Harbor

Nacional Hotel, Havana

Veranaro Beach, Cuba

A Main Street in Havana.

Monday, May 2	Arrive Nassau Sightseeing by private car will be provided Afternoon free for swimming, shopping, etc.	10:00 a.m.
Tuesday, May 3	Morning free Luncheon at the British Colonial Hotel Nassau will sail	 1:30 p.m. 7:00 p.m.
Wednesday, May 4	Enroute to Havana, arriving Dinner, Floor Show, and Dancing at the Tropicana outdoor night club	7:00 p.m. 9:00 p.m.
Thursday, May 5	Morning: A scientific program has been arranged at the University of Havana School of Medicine Afternoon: Sightseeing by private car will be provided Evening free	
Friday, May 6	*SS Nassau* will sail	5:00 a.m.
Saturday, May 7	Presidential Cocktail Party and Gala Dinner	6:00 p.m.
Sunday, May 8	Enroute to New York	
Monday, May 9	Arrive New York.	9:00 a.m.

The scientific program will be scheduled during the afternoons of April 30, May 1, May 4, May 6 and May 7 aboard ship. It is planned to have an inspection trip of things medical in Nassau, and to visit in Havana the Medical School and other places of medical interest.

Reservations may be arranged to depart the cruise from Nassau or Havana. Rates on request. Proof of citizenship is recommended for United States citizens. Customs requirements for other than United States citizens furnished on request. Custom allowances include $200.00 per person duty free, to include one gallon of spirituous liquor for United States citizens.

Rates. Steamship accommodations will range from $300.00 to $420.00 per person, basis of two in a room, to which must be added 10% Federal Tax, and various Port Taxes amounting to $3.85 per person. An additional charge of $26.00 per person will cover the following items:

1. Sightseeing by private automobile in Nassau.
2. Buffet outdoor luncheon, British Colonial Hotel, Nassau, including gratuities.
3. Transfers to and from the University of Havana.
4. Sightseeing by private automobile in Havana.
5. Transfers and dinner at Tropicana Night Club in Havana.

These special features will be of great interest to everyone in the party. The Tropicana Night Club, located amid the most beautiful and unusual setting, will be one of the real highlights of the shore excursions. Perhaps there is nothing comparable to this in the world.

As arrangements and reservations must be made well in advance, it is recommended that you immediately contact the cruise director, Mr. J. P. Sims, Jr., Raymond-Whitcomb, Inc., 1600 Walnut Street, Philadelphia 3, Pa. Plans of the *Nassau* and particulars will be forwarded. Accommodations will be assigned as received, and early application is important.

OBITUARIES

DR. CRAWFORD R. GREEN

Crawford Richmond Green, M.D., F.A.C.P., was born in Troy, N. Y., Sept. 8, 1881, and died in his native city on Aug. 16, 1954. He had retired from practice on July 26, 1952, because of a cerebral thrombosis.

After receiving his A.B. degree from Brown University in 1902 and his M.D. from New York Homeopathic Medical College and Hospital in 1906, Dr. Green interned at the Metropolitan Hospital in New York City. He then became Assistant House Physician and House Physician at the Cumberland Hospital in Brooklyn during 1906–07. Moving to northern New York State at this time, Dr. Green served as Neurologist and Pediatrist at the Albany Homeopathic Hospital for eight years and as Consulting Physician to the Memorial Hospital in Albany from 1923–37. For 33 years he was a member of the staff of the Samaritan Hospital in Troy, being Attending Physician from 1919 until 1947 and Consulting Physician from 1947 until his retirement. He was also Medical Director of the James A. Eddy Memorial Foundation from 1928 until 1952. Other former appointments of Dr. Green included those of Attending Physician for Russell Sage College, Director of the Babies' Milk Station, and Pediatrist at Leonard Hospital.

Dr. Green was a member of the Rensselaer County Medical Society, Medical Society of the State of New York, American Medical Association, Homeopathic Medical Society of the State of New York, American Institute of Homeopathy, and Phi Beta Kappa, Phi Alpha Gamma, and Delta Phi fraternities. A Diplomate of the American Board of Internal Medicine, he had been a member of the American College of Physicians since 1929.

Dr. Green was very highly respected by his colleagues in Troy and the surrounding county, and his passing will be felt deeply by his colleagues, patients and many friends.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. HENRY M. HENSEN

Henry Mathies Hensen, M.D., F.A.C.P., was drowned at Ocean City, Md., on July 17, 1954. Dr. Hensen was vacationing at Ocean City at the time of the fatal accident.

Baltimore, where he was born in 1904, was Dr. Hensen's home during the greater part of his life. After receiving his elementary education in Baltimore, he attended Gettysburg College, from which he graduated with a B.S. degree in 1929. In 1933 he was graduated from the Johns Hopkins University School of Medicine. Thereafter Dr. Hensen remained in Baltimore for his hospital training, serving as an intern and later an assistant resident physician at the Union Memorial Hospital from 1933 to 1935, and from 1935 through 1936 he was resident physician at the Hospital for the Women of Maryland. From 1936 to the time of his death, Dr. Hensen carried on a practice of general medicine in Baltimore, except for a period of three years of military service, namely from January, 1951, to February, 1954, most of which service was at the U. S. Army Hospital in Berlin. At that post Dr. Hensen was Chief of the Medical Service and held the rank of Major.

Dr. Hensen became a Fellow of the American College of Physicians in 1941.

R. CARMICHAEL TILGHMAN, M.D., F.A.C.P.,
Governor for Maryland

DR. HARRIS V. LILGA

Dr. Harris Vincent Lilga, F.A.C.P., was born on Sept. 18, 1909, at Lexington, Nebr., and died from accidental drowning in a motorboat tragedy on Aug. 10, 1954, on storm-tossed Walloon Lake, Mich.

Dr. Lilga attended Kearney State College in Nebraska and obtained his B.S. and M.D. degrees from the University of Nebraska in 1935. He interned at the University of Nebraska Hospital, Omaha, from 1935–36. He was a Resident in Psychiatry from 1936–38 at the Sheppard and Enoch Pratt Hospital, Towson, Md., and a Fellow in Internal Medicine from 1938–40 at the Cleveland Clinic Hospital.

He was a member of the staff at the Little Traverse Hospital from 1940–43. He served during the Second World War with a rank of Captain, and, thereafter, returned to the staff of the Little Traverse Hospital in Petoskey, Mich. His chief work was in internal medicine and gastroenterology on the staff of the Medical Department of the Burns Clinic.

He was a member of the Northern Michigan County Medical Society, Michigan State Medical Society, American Medical Association, and a Fellow of the American College of Physicians since 1945.

During Dr. Lilga's residence in Petoskey, he fulfilled in a most capable manner all the attributes which one hopes a physician would have. He was a most interested citizen, participating in many of the community problems, and was active in medical circles. Above all, he was a most considerate, conscientious, untiring, and understanding man, capable in his evaluation and care of his patients. He frequently gave of his knowledge to other physicians in the community and kept abreast of recent advances in medicine through extensive reading and the attendance at medical meetings and advanced courses.

Outside of his practice, Dr. Lilga was interested in painting and in wood carving. He produced many outstanding pieces of furniture, as well as several fine paintings.

He is survived by his wife and three daughters.

H. M. Pollard, M.D., F.A.C.P.,
Governor for Michigan

DR. ELLIOTT F. MAGUIRE

Dr. Elliott Francis Maguire (Associate) died in Philadelphia on July 18, 1954, in the Pennsylvania Hospital, Department for Mental and Nervous Diseases, where he was a patient.

Born in Philadelphia on April 16, 1915, he graduated from the University of Pennsylvania in 1939 with the degree of Bachelor of Arts and in 1943 received his M.D. degree from the University of Pennsylvania School of Medicine. After an internship at the Pennsylvania Hospital, Dr. Maguire became resident in pathology at the Abington (Pa.) Memorial Hospital during 1944–45 and was a Fellow in Internal Medicine at the Lahey Clinic, Boston, during 1947–48. He joined the faculty of the University of Pennsylvania School of Medicine in 1949 as Assistant Instructor and, at the time of his death, was Instructor in Medicine. He had been a member of the staff of the Pennsylvania Hospital since 1948 and was Associate Physician and Assistant to the Medical Director of the Hospital's Benjamin Franklin Clinic.

A Diplomate of the American Board of Internal Medicine, Dr. Maguire was a member of the Philadelphia County Medical Society, Medical Society of the State of Pennsylvania, American Medical Association, American Diabetes Association, and the World Medical Association. He was elected an Associate of the American College of Physicians in 1950.

DR. CHARLES A. McKENDREE

Dr. Charles Alphonso McKendree, F.A.C.P., died Sept. 10, 1954, in Greenwich, Conn. He was born Dec. 28, 1886, in Manchester, N. H., and received his A.B. degree from Dartmouth College in 1907 and his M.D. from Dartmouth Medical School in 1910. He then took postgraduate work at the New York Neurological Institute and in Paris and London in 1911–12. He served as Resident and later as Associate Physician in Cromwell Hall, Cromwell, Conn., from 1910–15. He was affiliated with the staff of Columbia University College of Physicians and Surgeons, where his initial appointment in 1915 was that of Instructor in Neurology, later advancing to Clinical Professor of Neurology, which he held until retiring in 1948. He served as Associate Professor of Neurology at the New York Post-Graduate Medical School and Hospital from 1920–25. He was Chief of Clinic of the Neurological Department of the Vanderbilt Clinic and later Attending Neurologist to the Vanderbilt Clinic from 1918 for some years. He was Attending Neurologist for the New York City Hospital from 1922–27.

Dr. McKendree was widely known and used as a Consulting Physician in Neurology for the Roosevelt, William Booth Memorial, Knickerbocker, St. Joseph (Far Rockaway), St. Luke's (Newburgh), Goshen, Berwind Maternity, North Hudson County and New Jersey Orthopaedic (Orange), and Greenwich (Conn.) Hospitals, Wassaic State School, and Stony Wold Sanatorium (Lake Kushaqua). He served in World War II and was discharged to inactive duty status as a Captain, (MC), USNR. He was the author of numerous papers concerning neurology and of the book *Neurological Examination*. He was President of the New York Neurological Society during 1938–39, a Fellow of the New York Academy of Medicine, a member of the New York County and State Societies, American Medical Association, the American Neurological and American Psychiatric Associations, the Association for Research in Nervous and Mental Disease, the Gamma Alpha Graduate Scientific Fraternity; Associate Member of the Phi Chi Medical Fraternity; member of the Military Order of the World Wars, the Society of the American Wars, and the Military Order of the Foreign Wars of the United States. He was a Qualified Psychiatrist of the State of New York, a Diplomate of the American Board of Psychiatry and Neurology, and a Fellow of the American College of Physicians since 1920.

Dr. McKendree was endowed with an unusually warm personality which drew to him many close friends, especially among young physicians. He was a sound advisor and a splendid teacher. Many physicians who have had the privilege of contact with Dr. McKendree will note with great sorrow his passing.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. CHARLES F. MOFFATT

Dr. Charles Frederick Moffatt, F.A.C.P., former Second Vice President, Regent and Governor of the College, died suddenly from an acute coronary thrombosis at his home in Montreal on Sept. 18, 1954.

Dr. Moffatt was born in Montreal in 1881, and after graduation from Montreal High School, proceeded to McGill University, receiving his A.B. degree in 1901 and M.D.C.M. in 1905. Following graduation he spent three years on the Resident Staff of the Royal Victoria Hospital in Montreal and after further study abroad returned to an appointment as Associate in Medicine in 1910. In 1934 he reached the rank of Physician, which he held until his appointment to the Honorary Attending Staff in 1946. After his early days as Admitting Officer, Dr. Moffatt became interested in the then relatively new science of electrocardiography, and was responsible through the subsequent years for the development of this service in the hospital, at the same time carrying a large part of the responsibility for clinical cardiology.

His interest in teaching led to his initial appointment as Assistant Demonstrator in Medicine at McGill University Faculty of Medicine in 1909, with further promotions to the rank of Assistant Professor, which he held until his retirement from active teaching in 1946.

In the First World War, Dr. Moffatt served with the rank of Captain in the Canadian Army Medical Corps, being attached to the Fourth Divisional Artillery and later to No. 1 Canadian General Hospital. In the Second World War, he acted as Consultant in Cardiology in the Montreal district.

Both before and after his retirement from the Attending Staff of the Hospital, he was active in the founding and development of the Montreal Cardiac Society and of the Canadian Heart Association.

Elected a Fellow of the American College of Physicians in 1929, he devoted much time and energy to its problems, being the Governor for the Province of Quebec for eight years, a Regent of the College for the next six years, and Second Vice President in 1952; during these periods of service he consistently represented and watchfully guarded the interests of the Canadian Fellows.

Dr. Moffatt gave generously of his time and of himself in the care of the sick, in the teaching of students and interns, and in his activities on behalf of his confreres. His death marks the passing of another of those unselfish physicians who have so greatly contributed to the progress of the College from its early days to its present firmly established position.

WALTER DEM. SCRIVER, M.D., F.A.C.P.,
Governor for Quebec

COL. BERTRAM H. OLMSTED

Col. Bertram Henry Olmsted, (MC), USA, Retired, F.A.C.P., died of arteriosclerosis and congestive heart failure in the Letterman Army Hospital, San Francisco, Calif., on Jan. 15, 1954.

A native of Pennsylvania, where he was born on June 6, 1880, Col. Olmsted attended Bucknell University, where he received the degree of Bachelor of Science in 1907. Four years later he obtained his degree of Doctor of Medicine from the University of Michigan Medical School. Commissioned in the Medical Corps of the U. S. Army in August, 1917, Col. Olmsted experienced almost 27 years of Army service, retiring June 30, 1944. Highlights of his Army career that encompassed two world wars included acting as Assistant Chief of Medical Service at the Letterman Army Hospital and as Chief of Medical Service at Colon Hospital, Cristobal, C. Z., and at the Station Hospital, Fort Lewis, Wash.

Col. Olmsted was a member of the American Medical Association, Sigma Alpha Epsilon, Nu Sigma Nu, and Alpha Omega Alpha fraternities. He had been a Fellow of the American College of Physicians since 1932.

DR. HENRY A. RAFSKY

Dr. Henry Aaron Rafsky, F.A.C.P., died on July 31, 1954, at Atlantic Beach, N. Y., from carcinoma of the colon.

Dr. Rafsky was born in New York City on June 28, 1890. He received his M.D. from Bellevue Hospital Medical College in 1913 and interned at the Beth Israel and Harlem Hospitals from 1913 to 1915. He was an Instructor in Medicine at the New York University Post-Graduate Medical School, 1921–23, and Clinical Professor of Medicine, New York University College of Medicine from 1947–54.

Dr. Rafsky was the author of numerous publications concerning metabolic diseases and gastroenterology. He was Associate in Metabolism and Chief of the Metabolic Clinic, 1922–30, Associate Attending Gastroenterologist, 1930, Attending Gastro-

enterologist, and Consultant Gastroenterologist at the Beth Israel Hospital. He served as Chief of the Gastroenterological Clinic in 1925, Associate Gastroenterologist, and Consultant Gastroenterologist at the Lenox Hill Hospital. He was Visiting Physician and President of the Medical Board of the Home and Hospital of the Daughters of Jacob in 1925; he had been Consultant Gastroenterologist to the Rockaway Beach Hospital since 1935.

Dr. Rafsky was a Fellow of the New York Academy of Medicine, a member of the New York County Medical Society, Medical Society of the State of New York, the New York Gastroenterological Association, and the National Society for the Advancement of Gastroenterology; he was the official representative of the A.M.A. Section on Gastroenterology and Proctology at the 1937 International Congress of Gastroenterology in Paris. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1930.

Dr. Rafsky made numerous contributions to medical practice, and his loss will be deeply felt by his colleagues and patients.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. H. R. RYAN, SR.

Harry Richard Ryan, Sr., M.D., F.A.C.P., of Rutland, Vt., a Fellow of the American College of Physicians since 1925 and a Life Fellow since 1940, died in Sarasota, Fla., on March 19, 1954, at the age of 71 years.

Dr. Ryan was born Dec. 25, 1882, in Rutland, and received his M.D. degree from the University of Vermont College of Medicine in 1904. Following a year's internship in the New York Lying-in Hospital, he began the practice of medicine in Rutland and continued fifty years of uninterrupted practice to the time of his death.

He was Chief of the Medical Staff at the Rutland Hospital for more than a decade before resigning about ten years ago. He was a Member of the Staff at the Proctor Hospital and a Member of the Consulting Staff at the Rutland Hospital at the time of his death, as well as a Medical Consultant to the Vermont Marble Company. He was a former Vice President and Secretary of the Rutland County Medical Society, a member of the Rutland Clinical Society, Vermont State Medical Society, and the American Medical Association, as well as the New York Society for Anesthetists. For many years he served as the Acting Chief Medical Officer of the Rutland Railroad and as a Medical Examiner for the Fraternal Order of Eagles for almost fifty years.

In the death of Dr. Ryan, the medical profession lost one of its most beloved members. He was a man greatly admired by his professional colleagues and the community in which he practiced.

WILLIAM A. PRATT, M.D. (Associate)

BRIG. GEN. JAMES STEVENS SIMMONS

Brig. Gen. James Stevens Simmons, (MC), USA, Retired, F.A.C.P., Dean of the Harvard School of Public Health, died suddenly on July 31, 1954, at the age of 64. Here was a man who devoted his life to the prevention of illness and the conservation of human resources and health. "Steve," as he was known to his intimate friends, was responsible for leading an effective crusade for preventing illness and maintaining the health of the men and women in the Army of the United States during World War II. That he discharged this responsibility in a manner that will continue to make world's history is a matter of public record. Everyone who had the privilege of knowing him realized that this man had a passion for preventing illness, and he used every known weapon at his command to fight disease before it could get under way. He looked upon all disease as a failure on the part of medical science;

and he realized that a sick man was a liability—to himself, to his family, and to the community.

After thirty years of distinguished service in the Army Medical Corps, Gen. Simmons became the Dean of the School of Public Health at Harvard University; and Dr. Conant cited him as "the imaginative rebuilder of the Harvard School of Public Health" when the honorary degree of Doctor of Science was awarded to him by Harvard University.

His career in the Army was a long and distinguished one. By sheer hard work, devotion to service, and loyalty to the cause of preventive medicine, Gen. Simmons made his lasting mark. None will deny that his industry, energy and application were a credit not only to his country, his family and his friends but to himself as well. Many honors were bestowed upon him in recognition of his contributions to others. His advice and counsel were sought by many, and those who were fortunate enough to receive his advice realized that a man of experience was speaking from the heart.

"Steve" had many assets, but one of the greatest of them all was his devoted wife Blanche. She contributed much to his success and to his great understanding of human affairs. One of his close friends and colleagues said "I do not need to tell you how much we all miss Blanche and Steve as our academic year gets underway. The faculty is doing its best to carry on." What greater tribute can be paid to any man and his wife?

Gen. Simmons was an active member of the College, of which he had been a member since 1926, and contributed his services to the annual programs and post-graduate courses. He was the first recipient of the James D. Bruce Memorial Award in Preventive Medicine of the American College of Physicians—a distinction that was well earned and well deserved.

"Steve" will be missed most by those who knew him best, but he will be missed by all who had the privilege of knowing him.

CHESTER S. KEEFER, M.D., F.A.C.P.

DR. WILLIAM D. WEIS

William Daniel Weis, M.D., F.A.C.P., who died April 18, 1954, in Munster, Ind., of bacterial endocarditis and valvular heart disease, was born to Jacob A. and Julia A. (Long) Weis at Hanover Center, Lake County, Ind., Nov. 28, 1873. Except for a short time of living in Jasper County, he lived in Crown Point until maturity.

At an early age, he learned the machinist trade. While in his second year of high school, he took an examination for a teacher's license and taught school in Hanover Township for two years. He then went to Valparaiso College as a student. In his second term there, he was offered, and accepted, a teaching position. He was Professor of Biology and Comparative Anatomy during 1896–1902, and of Bacteriology from 1898–1902; he also served as Professor of Pathology and Bacteriology at Chicago College of Medicine and Surgery from 1901–04. In six years he graduated in the civil engineering and scientific departments of Valparaiso. In the next two years, after special studies at Chicago University, he received the degree of Doctor of Medicine from Chicago College of Medicine and Surgery, now the Department of Medicine of Loyola University. He had an internship at St. Margaret Hospital, Hammond, in 1904, later becoming Secretary and President of the Staff.

While active in a medical career, Dr. Weis organized and conducted the City Health Department of Hammond for ten years, 1908–18. He was the Chief Medical Officer of the Draft Board during World War I. He was a member of the Board of Managers, Lake County Tuberculosis Sanatorium. In 1934, Dr. Weis was appointed by the Lake County Commissioners to develop and conduct a modern County Health Department. This activity received his full-time service until 1952. He was

President of the Lake County Medical Society in 1909, of the Lake Michigan Sanitary Association in 1914, and of the Hammond Medical Society in 1928. He was a member of the Indiana State, American Medical, and American Public Health Associations. He had been a Fellow of the American College of Physicians since 1926.

To the prevention of disease Dr. Weis devoted many years of his fruitful life. Organizations for the promotion of good things in various phases of life have profited by his effective attention.

JAMES O. RITCHEY, M.D., F.A.C.P.,
Governor for Indiana

DR. WALTER I. WERNER

Dr. Walter I. Werner, Governor of the American College of Physicians for New Mexico since 1949, lost his life in a Braniff International Airways crash at Mason City, Iowa, on August 22, 1954.

Dr. Werner was born at Covington, Ky., February 6, 1898, took his pre-medical training at Fordham University and received his medical degree from the University of Maryland in 1923. He was an intern at Mount Sinai Hospital, Cleveland, 1923–24, and extern at the Baltimore City Hospital, 1922–23. He did postgraduate work at the Trudeau School of Tuberculosis and studied electrocardiography at Western Reserve University under Dr. Harold Feil, F.A.C.P. His practice was largely restricted to internal medicine and allergy. He was certified by the American Board of Internal Medicine in 1939, became a Fellow of the American College of Physicians in 1941, and became the College Governor for New Mexico in 1949. For many years he had been Director of Clinical Research (Tuberculosis), Presbyterian Medical Center, Consultant in Internal Medicine and Allergy to the Veterans Administration Hospital and Lecturer in Allergy to Nurses, St. Joseph Sanatorium and Hospital.

Dr. Werner was a member of the American Trudeau Society, American Heart Association, Southwestern Medical Association, Bernalillo County Medical Society, New Mexico State Medical Association and the American Medical Association. He had been a Fellow of the American College of Physicians since 1941. He is survived by his wife, Dr. Ly Werner.

Dr. Werner performed his services for the American College of Physicians with capability and good judgment. He engendered early the confidence and affection of all his confreres.

DR. NATHAN DAVID WILENSKY

Dr. Nathan David Wilensky (Associate), Brooklyn, N. Y., died Aug. 30, 1954, of malignant hypertension and uremia.

He was born in New York City on Nov. 10, 1907, and obtained his medical degree in 1931 from the New York Homeopathic Medical College and Flower Hospital. He served as an intern at the Kings County Hospital from 1931–33, as Assistant Visiting Physician in 1933, and as Associate Visiting Physician, becoming Chief of the Peripheral Vascular Clinic there in 1952. He became Assistant Visiting Physician in 1933 and Associate Visiting Physician in 1939 and Chief of the Peripheral Vascular Clinic of the Jewish Sanitarium and Hospital for Chronic Diseases in 1953. Dr. Wilensky served as Assistant Attending Physician from 1940–54 and as Assistant, Peripheral Vascular Clinic, 1935–54, in the Maimonides Hospital. He was Attending Visiting Physician from 1949–50 in the Harbor Hospital.

Dr. Wilensky was a member of the New York Academy of Science, Bronx Society of Internal Medicine, Kings County Medical Society, Medical Society of the State of New York, American Medical Association, American Diabetes Association,

American Heart Association, American Federation for Clinical Research, American Gerontological Society, American Association for the Advancement of Science, and the American Association for the Study of Arteriosclerosis. He was a Diplomate of the American Board of Internal Medicine and a Founding Fellow of the Clinical Society of the New York Diabetes Association. He was elected to Associateship in the American College of Physicians in 1952.

The passing of Dr. Wilensky will be mourned by his family, colleagues and friends.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JOHN POWELL WILLIAMS

Dr. John Powell Williams, F.A.C.P., Chief of the Medical Service, Veterans Administration Hospital, Richmond, Va., died Sept. 1, 1954, after a long career devoted to the practice of internal medicine.

Dr. Williams was born in Richmond on Oct. 25 [illegible] After interruptions caused by military service on the Mexican Border and in [illegible] his education with the receipt of an A.B. degree from t[illegible] 1922, and an M.D. degree from the University's Depa[illegible] He then served as intern and resident at St. Luke's Hos[illegible] ing which he entered practice in his native city. Dr. W[illegible] at the Medical College of Virginia from 1925 until his [illegible] appointment as Professor of Clinical Medicine. He al[illegible] sician in the College's Hospital Division.

During World War II, he served from 1942 to [illegible] of the Medical Service in the 45th General Hospital, [illegible] operation overseas in Naples. Upon his return from It[illegible] of the Medical Service, Kennedy General Hospital, Men[illegible] tion. In recognition of his service, Dr. Williams recei[illegible]

In early 1946, he accepted appointment in the [illegible] Surgery, Veterans Administration, with assignment in [illegible] Medical Service to the Veterans Administration Hospi[illegible] on this duty until his death.

Dr. Williams was a Diplomate of the American Bo[illegible] since 1951, an official examiner of the Board. He wa[illegible] Academy of Medicine (Ex-President), Medical Society [illegible] cal Association, Southern Medical Association, Tri-St[illegible] the Constantinian Society. He had been a Fellow of the American College of Physicians since 1947.

Dr. Williams had a long and distinguished career in internal medicine in the city of his birth. He was a brilliant clinician and an inspiring teacher. His loss will be keenly felt by his colleagues, his patients, and his many friends.

J. T. BOONE, Vice Admiral, (MC), U. S. Navy, Rtd.,
Chief Medical Director,
Governor for the Veterans Administration

Pro-Banthine: For Anticholinergic Action in the Gastrointestinal Tract

Combined neuro-effector and ganglion inhibiting action of Pro-Banthine consistently controls gastrointestinal hypermotility and spasm and the attendant symptoms.

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[illegible]f the gastroin-[illegible]ound wide use[1] [illegible]unctional diar-[illegible]ative colitis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.

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For the average patient one tablet of Pro-Banthine (15 mg.) with each meal and two tablets (30 mg.) at bedtime will be adequate. G. D. Searle & Co., Research in the Service of Medicine.

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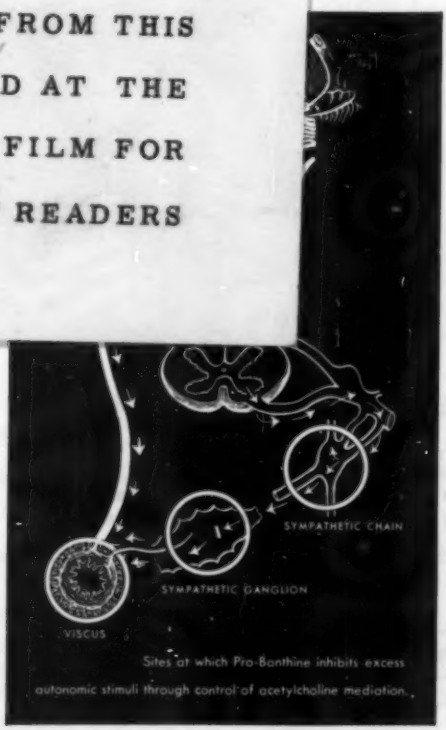

1. Schwartz I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

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During World War II, he served from 1942 to 1946 in the capacity of Chief of the Medical Service in the 45th General Hospital, U. S. Army, which was in operation overseas in Naples. Upon his return from Italy, he served briefly as Chief of the Medical Service, Kennedy General Hospital, Memphis, Tenn., until his separation. In recognition of his service, Dr. Williams received the Legion of Merit.

In early 1946, he accepted appointment in the Department of Medicine and Surgery, Veterans Administration, with assignment in the capacity of Chief of the Medical Service to the Veterans Administration Hospital, Richmond. He continued on this duty until his death.

Dr. Williams was a Diplomate of the American Board of Internal Medicine and, since 1951, an official examiner of the Board. He was a member of the Richmond Academy of Medicine (Ex-President), Medical Society of Virginia, American Medical Association, Southern Medical Association, Tri-State Medical Association, and the Constantinian Society. He had been a Fellow of the American College of Physicians since 1947.

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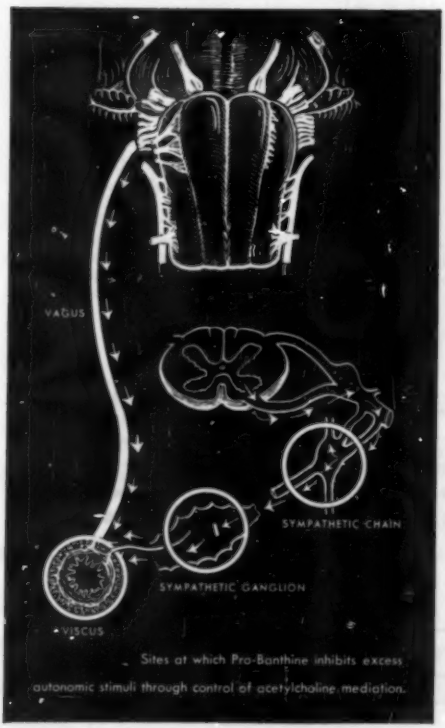
By controlling excess motility of the gastrointestinal tract, Pro-Banthine has found wide use[1] in the treatment of peptic ulcer, functional diarrheas, regional enteritis and ulcerative colitis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.



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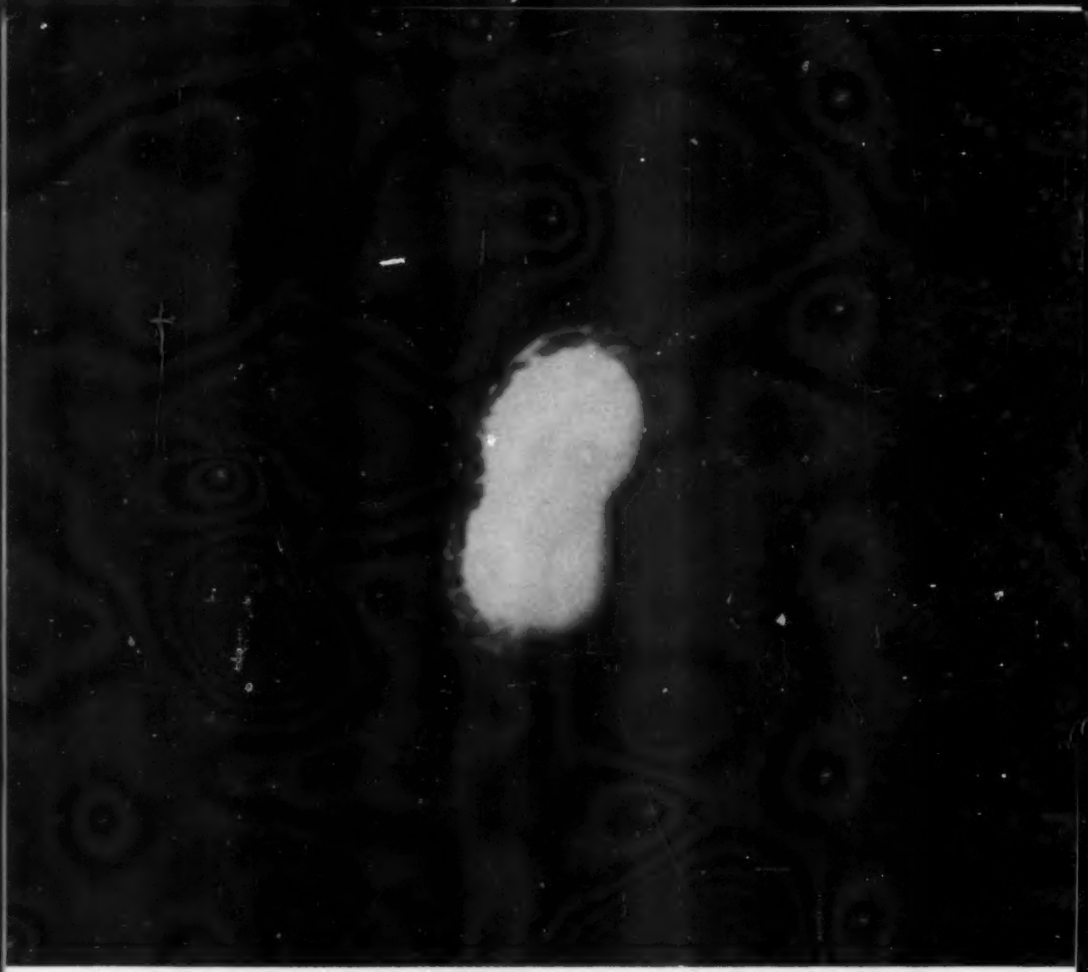

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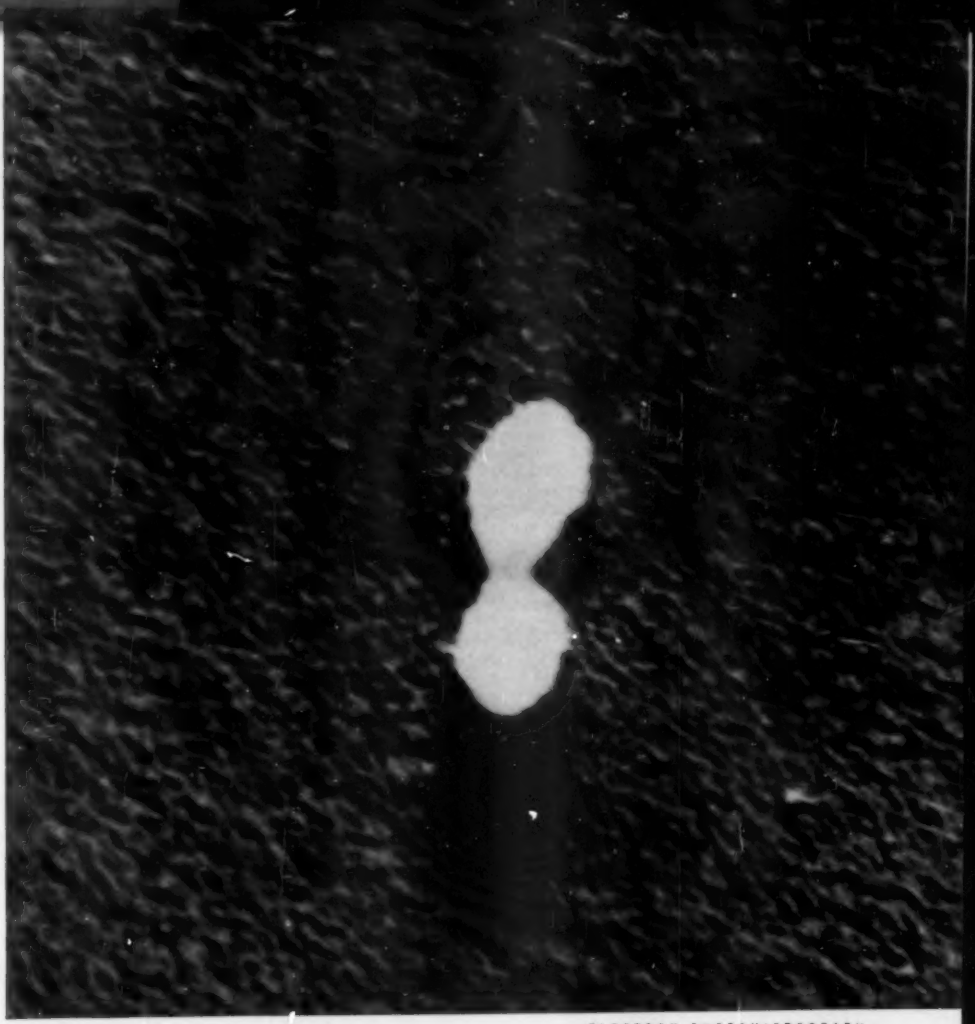

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1. McHardy and Browne: Sou. Med. J. 45:1139, 1952. 2. Lorber and Shay: Fed. Proc. 12:90, 1952.

Complete Bentyl bibliography on request.

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1. C. S. Davidson: Protein Metabolism With Particular Reference to Problems of Aging. Symposium on Problems of Gerontology, August 1954.
2. Brozek, J.: Changes of Body Composition in Man During Maturity and Their Nutritional Implications. Fed. Proc. 11:784 (1952).
3. Monroe, R. T.: Diseases in Old Age. Harvard University Press, Cambridge (1951).

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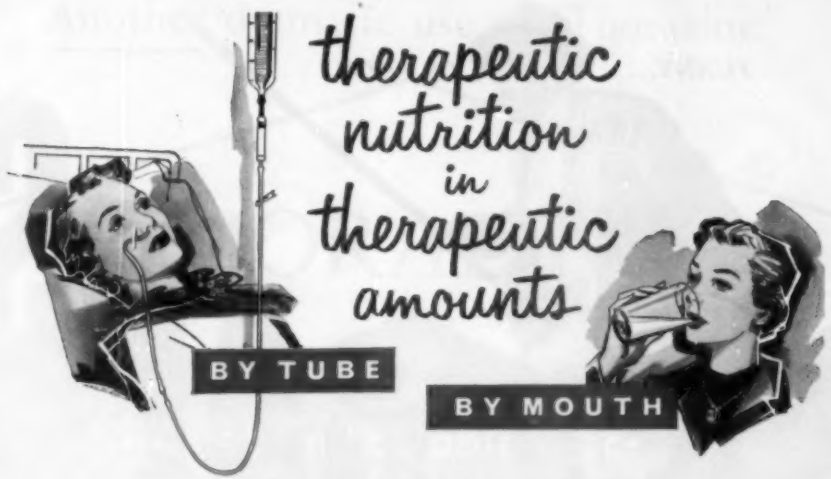

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Ascorbic acid	300 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Calcium pantothenate	40 mg.
Pyridoxine hydrochloride	5 mg.
Choline bitartrate	300 mg.
Folic acid	2.5 mg.
Vitamin B_{12} (crystalline)	4 mcg.
Iron (from ferrous sulfate)	15 mg.
Calcium	6.3 Gm.
Phosphorus	4.5 Gm.
Sodium	1.9 Gm.
Potassium	7 Gm.

Dilution for tube feeding:
1 cup Sustagen to 10 oz. water

Dilution for oral feeding:
1 cup Sustagen to 8 oz. water

*Therapeutic Nutrition, Publication No. 234, National Research Council.

Reports of steady weight gains with patients fed Sustagen* *exclusively* for more than 90 days attest its nutritional completeness.

By tube—

With Mead's Tube Feeding Set, using plastic tubing half the size of the smallest rubber tubing, Sustagen is easily administered without discomfort to your patients. The problems of diarrhea, cramps and nausea so long associated with tube feeding are virtually eliminated with Sustagen.

Sustagen also makes possible more complete nutrition for many patients for whom parenteral alimentation was heretofore the only practical and effective means available.

By mouth—

Sustagen mixes easily with water to make a delicious therapeutic food drink for your patients on liquid or restricted diets, underweight or undernourished persons, and when tube feeding is discontinued.

Available through drug stores in 1-lb. and 2¼-lb. cans, and to hospitals in 5-lb. cans.

MEAD MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U. S. A.

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